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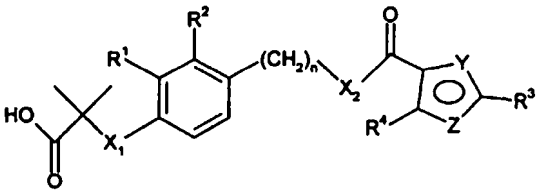
(54) Title: SUBSTITUTED OXAZOLES AND THIAZOLES DERIVATIVES AS HPPAR ALPHA ACTIVATORS



(I)

(57) Abstract: A compound of formula (I) and pharmaceutically acceptable salts, solvates and hydrolysable esters thereof wherein; X^1 represents O or S; R^1 and R^2 independently represent H, halogen, $-CH_3$ and $-OCH_3$; n represents 1 or 2; X_2 represents NH, NCH_3 or O; One of Y and Z is N, and the other is O or S; R^3 represents phenyl or pyridyl (wherein the N is in position 2 or 3) and is optionally substituted by one or more halogen, NO_2, NH_2, CF_3, OCF_3, OC_{1-6} straight or branched alkyl, C_{1-6} straight or branched alkyl, alkenyl or alkynyl with the provision that when R^3 is pyridyl, the N is unsubstituted; R^4 represents CF_3 or CH_3.

SUBSTITUTED OXAZOLES AND THIAZOLES DERIVATIVES AS HPPAR ALPHA ACTIVATORS

The present invention relates to certain novel compounds. In particular, the present invention relates to compounds that activate the alpha subtype of the human peroxisome proliferator activated receptor ("hPPAR alpha"). The present invention also relates to methods for preparing the compounds and methods for prevention or treatment of PPAR alpha mediated diseases or conditions.

Several independent risk factors have been associated with cardiovascular disease. These include hypertension, increased fibrinogen levels, high levels of triglycerides, elevated LDL cholesterol, elevated total cholesterol, and low levels of HDL cholesterol. HMG CoA reductase inhibitors ("statins") are useful for treating conditions characterized by high LDL-c levels. It has been shown that lowering LDL-c is not sufficient for reducing the risk of cardiovascular disease in some patients, particularly those with normal LDL-c levels. This population pool is identified by the independent risk factor of low HDL-c. The increased risk of cardiovascular disease associated with low HDL-c levels has not yet been successfully addressed by drug therapy (i.e., currently there are no drugs on the market that are useful for raising HDL-c >40%). (Bisgaier, C. L.; Pape, M. E. *Curr. Pharm. Des.* 1998, *4*, 53-70).

Syndrome X (including metabolic syndrome) is loosely defined as a collection of abnormalities including hyperinsulinemia, obesity, elevated levels of trigycerides, uric acid, fibrinogen, small dense LDL-c particles, and plasminogen activator inhibitor 1 (PAI-1), and decreased levels of HDL-c.

NIDDM is described as insulin resistance which in turn causes anomalous glucose output and a decrease in glucose uptake by skeletal muscle. These factors eventually lead to impaired glucose tolerance (IGT) and hyperinsulinemia.

Peroxisome Proliferator Activated Receptors (PPARs) are orphan receptors belonging to the steroid/retinoid receptor superfamily of ligand-

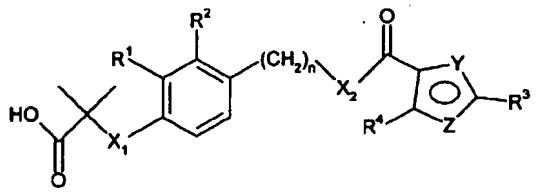
activated transcription factors. See, for example, Willson, T. M. and Wahli, W., Curr. Opin. Chem. Biol., (1997), Vol. 1, pp 235-241.

Three mammalian Peroxisome Proliferator-Activated Receptors have been isolated and termed PPAR-alpha, PPAR-gamma, and PPAR-delta (also known as NUC1 or PPAR-beta). These PPARs regulate expression of target genes by binding to DNA sequence elements, termed PPAR response elements (PPRE). To date, PPRE's have been identified in the enhancers of a number of genes encoding proteins that regulate lipid metabolism suggesting that PPARs play a pivotal role in the adipogenic signaling cascade and lipid homeostasis (H. Keller and W. Wahli, *Trends Endoodn. Met* 291-296, 4 (1993)).

Certain compounds that activate or otherwise interact with one or more of the PPARs have been implicated in the regulation of triglyceride and cholesterol levels in animal models. See, for example, U.S. Patents 5,847,008 (Doebber et al.) and 5,859,051 (Adams et al.) and PCT publications WO 97/28149 (Leibowitz et al.) and WO99/04815 (Shimokawa et al.).

Fibrates are a class of drugs which may lower serum triglycerides 20-50%, lower LDL-c 10-15%, shift the LDL particle size from the more atherogenic small dense to normal dense LDL-c, and increase HDL-c 10-15%. Experimental evidence indicates that the effects of fibrates on serum lipids are mediated through activation of PPAR alpha. See, for example, B. Staels et al., *Curr. Pharm. Des., 1-14*, 3 (1), (1997). Activation of PPAR alpha results in transcription of enzymes that increase fatty acid catabolism and decrease de-novo fatty acid synthesis in the liver resulting in decreased triglyceride synthesis and VLDL-c production/secretion. In addition, PPAR alpha activation decreases production of apoC-III. Reduction in apoC-III, an inhibitor of LPL activity, increases clearance of VLDL-c. See, for example, J. Auwerx et al., *Atherosclerosis, (Shannon, Irel.), S29-S37*, 124 (Suppl), (1996). PPAR alpha ligands may be useful for the treatment of dyslipidemia and cardiovascular disorders, see Fruchart, J.C., Duriez, P., and Staels, B., Curr. Opin. Lipidol. (1999), Vol 10, pp 245-257.

According to a first aspect of the invention there is provided a compound of formula (I) and pharmaceutically acceptable salts, solvates and hydrolysable esters thereof:



(I)

wherein;

X_1 represents O or S;

R^1 and R^2 independently represent H, halogen, $-CH_3$ and $-OCH_3$;

n represents 1 or 2;

X_2 represents NH, NCH_3 or O;

One of Y and Z is N, and the other is O or S;

R^3 represents phenyl or pyridyl (wherein the N is in position 2 or 3) and is optionally substituted by one or more halogen, NO_2, NH_2, CF_3, OCF_3, OC_{1-6} straight or branched alkyl, C_{1-6} straight or branched alkyl, alkenyl or alkynyl with the provision that when R^3 is pyridyl, the N is unsubstituted;

R^4 represents CF_3 or CH_3.

In another aspect, the present invention discloses a method for prevention or treatment of a human PPAR alpha ("hPPAR alpha") mediated disease or condition comprising administration of a therapeutically effective amount of a compound of this invention. hPPAR alpha mediated diseases or conditions include dyslipidemia including associated diabetic dyslipidemia and mixed dyslipidemia, syndrome X (as defined in this application this embraces metabolic syndrome), heart failure, hypercholesteremia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, and regulation of appetite and food intake in subjects suffering from disorders such as obesity, anorexia bulimia, and anorexia nervosa. Other diseases or conditions include inflammation. In particular, the compounds of this invention are useful in the treatment and prevention of cardiovascular diseases and

conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and mixed dyslipidaemia.

In another aspect, the present invention provides pharmaceutical compositions comprising a compound of the invention, preferably in association with a pharmaceutically acceptable diluent or carrier.

In another aspect, the present invention provides a compound of the invention for use in therapy, and in particular, in human medicine.

In another aspect, the present invention provides the use of a compound of the invention for the manufacture of a medicament for the treatment of a hPPAR alpha mediated disease or condition.

In another aspect, the present invention provides a method of treatment of a patient suffering from a hPPAR alpha mediated disease or condition comprising the administration of a therapeutically effective amount of a compound of the invention.

As used herein, "a compound of the invention" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or hydrolyzable ester thereof.

While hydrolyzable esters are included in the scope of this invention, the acids are preferred because the data suggests that while the esters are useful compounds, it may actually be the acids to which they hydrolyze that are the active compounds. Esters that hydrolyze readily can produce the carboxylic acid in the assay conditions or in vivo. Generally the carboxylic acid is active in both the binding and transient transfection assays, while the ester does not usually bind well but is active in the transient transfection assay presumably due to hydrolysis. Preferred hydrolysable esters are C_{1-6} alkyl esters wherein the alkyl group may be straight chain or branched chain. Methyl or ethyl esters are more preferred.

Preferably X_1 represents O.

Preferably one of R^1 and R^2 represents H with R^1 and R^2 both representing H being more preferred.

Preferably n represents 1.

Preferably X_2 represents NH.

Preferably Z represents N.

Preferably Y represents S.

Preferably R^3 is phenyl, optionally substituted. Preferably R^3 is mono or disubstituted. Preferably when R^3 is pyridyl the N is in the 2 position. R^3 preferably is monosubstituted in the para position and is more preferably phenyl. A preferred substituent is CF_3.

Preferably R^4 represents CH_3.

While the preferred groups for each variable have generally been listed above separately for each variable, preferred compounds of this invention include those in which several or each variable in Formula (I) is selected from the preferred, more preferred, or most preferred groups for each variable. Therefore, this invention is intended to include all combinations of preferred, more preferred, and most preferred groups.

Preferably, the compounds of formula (I) are hPPAR alpha agonists. As used herein, by "agonist", or "activating compound", or "activator", or the like, is meant those compounds which have a pKi of at least 6.0 to the relevant PPAR, for example hPPAR alpha, in the binding assay described below, and which achieve at least 50% activation of the relevant PPAR relative to the appropriate indicated positive control in the transfection assay described below at concentrations of 10^{-5} M or less. More preferably, the compounds of this invention achieve 50% activation of human PPAR alpha in the transfection assay at concentrations of 10^{-7} M or less.

Most preferably, the compounds of formula (I) are selective hPPAR alpha agonists. As used herein, a "selective hPPAR alpha agonist" is a hPPAR alpha agonist whose EC_{50} for PPAR alpha is at least 10 fold lower than its EC_{50} for PPAR gamma and PPAR delta. Such selective compounds may be referred to as "10-fold selective." EC_{50} is defined in the transfection assay described below and is the concentration at which a compound achieves 50% of its maximum activity. Most preferred compounds are greater than 100-fold selective hPPAR alpha agonists.

Preferred compounds of the invention include:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid ethyl ester

N-methyl-2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid ethyl ester

4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-carboxylic acid 4-(1-tertbutyloxycarbonyl-1-methylethoxy) benzyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-nitrophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-aminophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-aminophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[3,4-dichlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[3-fluoro-4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-bromophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-ethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-phenylthiazol-5-ylcarbonyl)amino]-methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-fluorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-chlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-methoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-acetylenylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethylphenyl]-oxazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethyl-2-pyridyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[2-methoxy-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(5-methyl-2-[4-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(5-methyl-2-[4-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(5-methyl-2-[3-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(5-methyl-2-[3-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid

More preferred compounds of the invention include:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid

N-methyl-2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-nitrophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[3,4-dichlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[3-fluoro-4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-bromophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-ethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-phenylthiazol-5-ylcarbonyl)amino]-methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-fluorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-chlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-methoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-acetylenylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethylphenyl]-oxazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethyl-2-pyridyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[2-methoxy-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

A particularly preferred compound of the invention is 2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]thiazol-5-yl-carbonyl)amino]methyl}phenoxy] propionic acid.

The preferred compound listed above is a selective hPPAR alpha agonist.

It will also be appreciated by those skilled in the art that the compounds of the present invention may also be utilized in the form of a pharmaceutically acceptable salt or solvate thereof. The physiologically acceptable salts of the compounds of formula (I) include conventional salts formed from pharmaceutically acceptable inorganic or organic acids or bases as well as quaternary ammonium acid addition salts. More specific examples of suitable acid salts include hydrochloric, hydrobromic, sulfuric, phosphoric, nitric, perchloric, fumaric, acetic, propionic, succinic, glycolic, formic, lactic, maleic, tartaric, citric, palmoic, malonic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, fumaric, toluenesulfonic, methanesulfonic, naphthalene-2-sulfonic, benzenesulfonic hydroxynaphthoic, hydroiodic, malic, steroic, tannic and the like. Other acids such as oxalic, while not in themselves pharmaceutically

acceptable, may be useful in the preparation of salts useful as intermediates in obtaining the compounds of the invention and their pharmaceutically acceptable salts. More specific examples of suitable basic salts include sodium, lithium, potassium, magnesium, aluminium, calcium, zinc, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, N-methylglucamine and procaine salts. References hereinafter to a compound according to the invention include both compounds of formula (I) and their pharmaceutically acceptable salts and solvates.

The compounds of the invention and their pharmaceutically acceptable derivatives are conveniently administered in the form of pharmaceutical compositions. Such compositions may conveniently be presented for use in conventional manner in admixture with one or more physiologically acceptable carriers or excipients.

While it is possible that compounds of the present invention may be therapeutically administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Accordingly, the present invention further provides for a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof together with one or more pharmaceutically acceptable carriers therefore and, optionally, other therapeutic and/or prophylactic ingredients.

The formulations include those suitable for oral, parenteral (including subcutaneous e.g. by injection or by depot tablet, intradermal, intrathecal, intramuscular e.g. by depot and intravenous), rectal and topical (including dermal, buccal and sublingual) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the compounds ("active ingredient")

with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets (e.g. chewable tablets in particular for paediatric administration) each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a other conventional excipients such as binding agents, (for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone), fillers (for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol), lubricants (for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica), disintegrants (for example, potato starch or sodium starch glycollate) or wetting agents, such as sodium lauryl sulfate. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein. The tablets may be coated according to methods well-known in the art.

Alternatively, the compounds of the present invention may be incorporated into oral liquid preparations such as aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, for example. Moreover, formulations containing these compounds may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents such as sorbitol

syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminum stearate gel or hydrogenated edible fats; emulsifying agents such as lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils) such as almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid. Such preparations may also be formulated as suppositories, e.g., containing conventional suppository bases such as cocoa butter or other glycerides.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of a sterile liquid carrier, for example, water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter, hard fat or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose and acacia.

The compounds may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion

exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

In addition to the ingredients particularly mentioned above, the formulations may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms. Moreover, it will be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician or veterinarian. In general, however, doses employed for adult human treatment will typically be in the range of 0.02-5000 mg per day, preferably 1-1500 mg per day. The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day. The formulations according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

The compound of formula (I) for use in the instant invention may be used in combination with other therapeutic agents for example, statins and/or other lipid lowering drugs for example MTP inhibitors and LDLR upregulators. The compounds of the invention may also be used in combination with antidiabetic agents, e.g. metformin, sulfonylureas and/or PPAR gamma agonists (for example thiazolidinediones such as e.g. Pioglitazone and Rosiglitazone). The compounds may also be used in combination with antihypertensive agents such as calcium channel antagonists and ACE inhibitors. The invention thus provides in a further aspect the use of a combination comprising a compound of formula (I) with a further therapeutic agent in the treatment of a hPPAR alpha mediated disease.

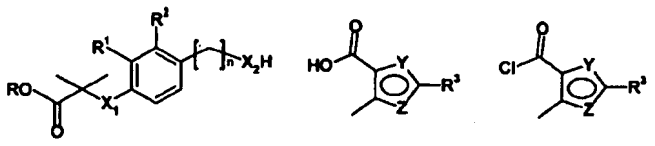
When the compounds of formula (I) are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optimally together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When combined in the same formulation it will be appreciated that the two compounds must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

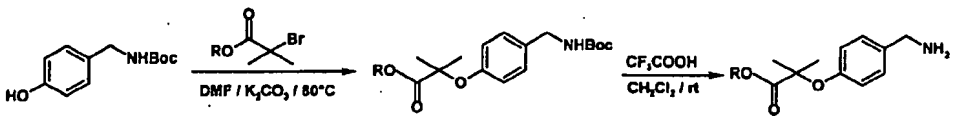
When a compound of formula (I) is used in combination with a second therapeutic agent active against the same hPPAR alpha mediated disease, the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

Compounds of this invention may be conveniently prepared by a general process wherein a moiety like **(A)** is coupled to an acid **(B)** using a peptide coupling reaction or by alkylation of **(A)** using a suitable non nucleophilic amine with an acid chloride **(C)**. Preferably, R is 1-6 alkyl which can be hydrolyzed off to give an acid of Formula (I), or if readily hydrolyzable, the resulting ester can be administered.



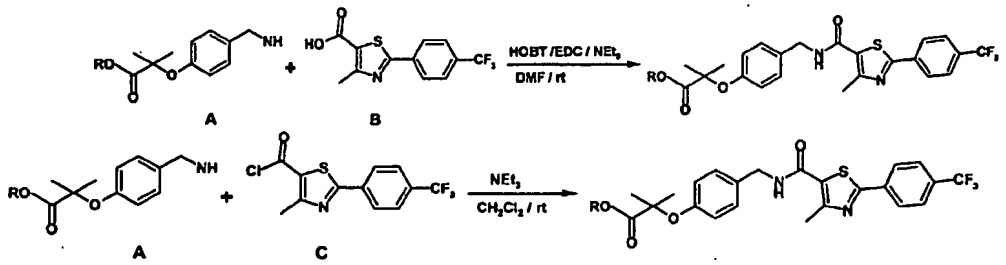
A B C

A preferred synthesis of **(A)** when X_1 is O and X_2 is NH (and R^1 and R^2 are H) is:



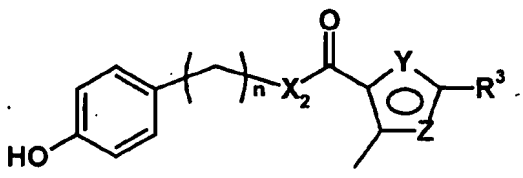
A

Note that this synthesis is preferably carried out with the amine where the alcohol function is already alkylated with the acid side chain protected by R. For example, when n is1, X_1 is O, X_2 is NH, Y is S, Z is N, R^1 and R^2 are H, and R^3 is 4-F_3C-phenyl:



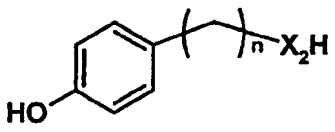
Some of the intermediates of type **A** are commercially available while others can be synthesized by techniques apparent to a person skilled in the art. The synthesis of intermediates of type **B** and **C** are illustrated below.

Compounds of the invention may be made by an alternative method in which compounds of formula **(D)** are reacted with ethyl 2-bromo-2 methyl propionate to produce the ethyl ester of the compound of formula (I) which may be hydrolysed to produce the free acid.



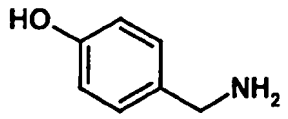
D

Compounds of formula **(D)** may be prepared from the reaction between compounds of formula **(B)** and compounds of formula **(E)** with HOBT / EDC / NEt_3 when X_2 is NH or NCH_3 or DIC / DMAP / NEt_3 when X_2 is O.



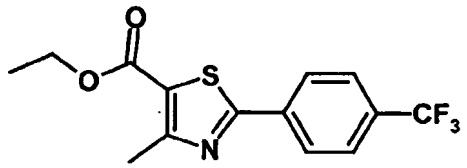
E

The invention is further illustrated by the following examples which should not be construed as constituting a limitation thereto.



Intermediate 1 :

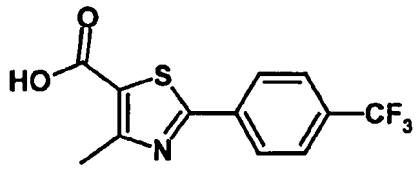
The procedure was as described in Stout, D. M. *J. Med. Chem.* **1983**, *26(6)*, 808-13. To 4-methoxybenzyl amine (25g, 0.18 mol; Aldrich) was added 46% HBr in H_2O (106ml, 0.9 mol; Aldrich). The reaction was refluxed overnight, then the reaction cooled to 0°C and neutralized to pH7 slowly with $KOH_{(s)}$. The reaction was allowed to stir for ~30 min, then the solid filtered and dried. The solid was redissolved in hot MeOH, filtered and the solution cooled to afford 19g (85%) intermediate **1**. ^1H NMR (DMSO-d_6): δ 8.0 (bs, 1H), 7.2 (d, 2H), 6.75 (d, 2H), 3.85 (s, 2H), 3.50 (bs, 2H).



Intermediate 2:

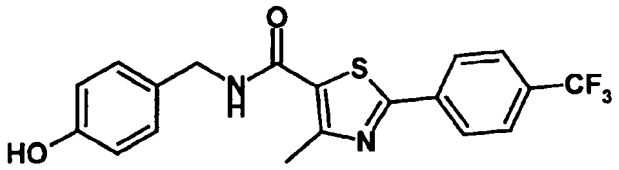
A solution of ethyl 2-chloroacetoacetate (35.3g, 29.7mL, 0.21 mol) and 4-(trifluoromethyl)thiobenzamide (44g, 0.21 mol) in EtOH (300mL) was refluxed overnight. After cooling to room temperature the solvent was removed in vacuo.

The final product (intermediate **2**) was recrystallized from a minimum of MeOH to afford 40g (59%) of final product as a white solid. ^{1}H NMR ($CDCl_3$): δ 8.10 (d, 2H), 7.70 (d, 2H), 4.40 (q, 2H), 2.80 (s, 3H), 1.4 (t, 3H).



Intermediate 3:

To intermediate **2** (1.84g, 5.8 mmol) in THF was added 1N LiOH (6mL, 6 mmol) and the reaction stirred at rt. After ~3h, the reaction was neutralized with 1N HCl, extracted 3 x 100 mL EtOAc, dried over Na_2SO_4, filtered and the solvent removed under vacuum to afford 1.5g (89%) intermediate **3** as a white solid. ^{1}H NMR (DMSO-d_6): δ 13.55 (bs, 1H), 8.25 (d, 2H), 7.95 (d, 2H), 2.75 (s, 3H).



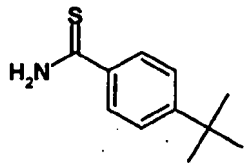
Intermediate 4:

To intermediate **3** (1g, 7 mmol) in CH_2Cl_2/DMF (1:1) was added HOBT (565mg, 4.2 mmol; Aldrich), EDC (800mg, 4.2 mmol; Aldrich) and intermediate **1** (860mg, 7 mmol). The reaction was stirred at rt for 18h. The solvent was removed *in vacuo*, treated with H_2O and extracted 3x 100mL CH_2Cl_2. The organic phases combined and washed with 1N HCl, dried over Na_2SO_4, filtered and evaporated to afford a mixture (*N*-substituted and *N,O*-substituted). The mixture was dissolved in MeOH and treated with 1N NaOH. The reaction was stirred 18h at 50°C. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2, washed with H_2O, and dried over Na_2SO_4. The solvent was evaporated and the residue chromatographed (CH_2Cl_2/MeOH: 99/1) to afford 610mg (47%) of intermediate **4** as a white solid. ^{1}H NMR (DMSO-d_6): δ 9.30 (s, 1H), 8.80 (t, 1H), 8.20 (d, 2H), 6.70 (d, 2H), 4.35 (d, 2H), 2.6 (s, 3H).

General procedure 1 for the preparation of substituted thiobenzamides

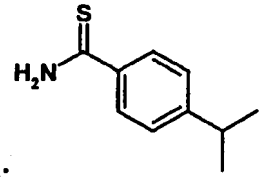
To a solution of P_4S_{10} (0.2 mmol) in toluene (100mL) was added $NaHCO_3$ (2 mmol) and the mixture heated to reflux for ca. 30min. The substituted

benzamide (1 mmol) was added and the reaction stirred at 90°C for 1h. The reaction was then evaporated to dryness, treated with brine (100mL) and extracted with CH_2Cl_2 (2 X 50mL). The organic phase dried, filtered, and evaporated to afford the final product.



Intermediate 5:

The title compound was prepared as described in general procedure 1 to afford an orange solid (49%). ^1H NMR ($CDCl_3$): δ 7.7 (d, 2H), 7.4 (bs, 1H), 7.3 (d, 2H), 7.0 (bs, 1H), 1.2 (s, 9H).



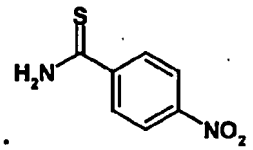
Intermediate 6:

The title compound was prepared as described in general procedure 1 to afford an orange solid (26%).

Mp: 150°C

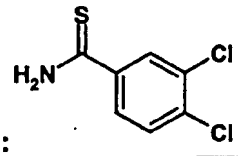
General procedure 2 for the preparation of substituted thiobenzamides

To the substituted benzonitrile (1 mmol) in DMF (30mL) is added dropwise DMF (21mL) saturated with $HCl_{(g)}$ during 1 min. Thioacetamide (2 mmol) is then added and the reaction heated to 100°C for 1h. $HCl_{(g)}$ is bubbled in for ca. 1 min and the stirring continued at 100°C for another 18h. The reaction cooled to rt, treated with ice and extracted with Et_2O (3 x 250mL). The organic phase was washed with H_2O (3 x 300mL), dried over Na_2SO_4, filtered, and evaporated to dryness. The residue was washed with a mixture of isopropyl ether/pentane (1:3) to afford the final product.



Intermediate 7:

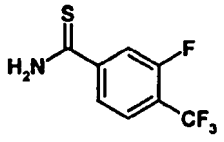
The title compound was prepared as described in general procedure 2 to afford an orange solid (83%). ^{1}H NMR (DMSO-d_6): δ 10.1 (bs, 1H), 9.7 (bs, 1H), 8.1 (d, 2H), 7.9 (d, 2H).



Intermediate 8:

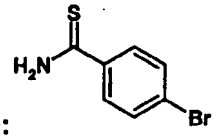
The title compound was prepared as described in general procedure 2 to afford a yellow solid (45%).

MS m/z 207 (M+1)



Intermediate 9:

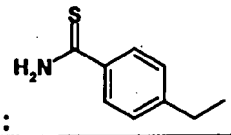
The title compound was prepared as described in general procedure 2 to afford an orange solid (84%). ^{1}H NMR (DMSO-d_6): δ 10.5 (bs, 1H), 10.05 (bs, 1H), 8.1 (m, 3H).



Intermediate 10:

To 4-bromobenzonitrile (1 mmol) was added the diethyldithiophosphate (1.2 equiv.). To the suspension was added H_2O (ca. 100mL) and the reaction heated to 80°C for ca. 2h. The reaction cooled to rt and extracted with Et_2O (3 x 100mL). The oganic phase was washed with sat. $NaHCO_3$, dried over $NaSO_4$ and evaporated to dryness leaving a yellow solid. The solid was rinsed with isopropyl ether and collected by filtration to afford the title compound as a yellow solid (55%).

MS m/z 214

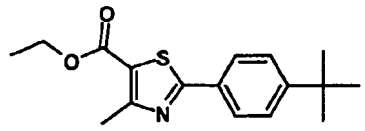


Intermediate 11:

To the 4-ethylbenzamide (1 mmol) in toluene heated to reflux, was added Laweson's reagent (1 equiv.). After the addidition was complete, the reaction was refluxed for 2h. The reaction cooled to rt, treated with Et_2O, washed with H_2O and the organic phase dried over Na_2SO_4. The solution filtered, evaporated to dryness and the residue chromatographed with CH_2Cl_2/MeOH (98:2) to afford 3g of the title compound as a yellow solid (55%). ^1H NMR (DMSO-d_6): δ 9.8 (bs, 1H), 9.4 (bs, 1H), 7.8 (d, 2H), 7.2 (d, 2H), 2.6 (q, 2H), 1.2 (t, 3H).

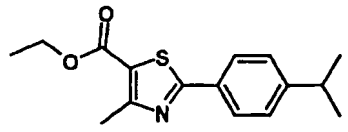
General procedure 3 for the preparation of 2-substituted phenyl-4-methyl-1,3-thiazole-5-caboxylic acid ethyl esters

To a solution of the substituted thiobenzamide (1 mmol) in EtOH (100 mL) was added ethyl 2-chloroacetoacetate (1.1 mmol) and the mixture heated to reflux overnight. The reaction is cooled to room temperature and the solvent evaporated. The solid is crystallized from Et_2O or hexane to afford the final product.



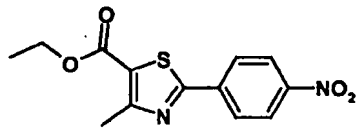
Intermediate 12:

Intermediate **5** was reacted as described in general procedure 3 to afford the title compound as an off-white solid (95%). ^1H NMR ($CDCl_3$): δ 8.0 (d, 2H), 7.55 (d, 2H), 4.45 (q, 2H), 3.85 (s, 3H), 2.5 (t, 3H), 1.45 (s, 9H).



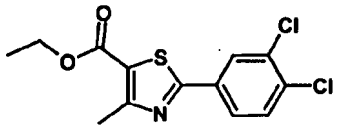
Intermediate 13:

Intermediate **6** was reacted as described in general procedure 3 to afford the title compound as an off-white solid (97%). ^1H NMR ($CDCl_3$): δ 7.85 (d, 2H), 7.25 (d, 2H), 4.30 (q, 2H), 2.90 (st, 1H), 2.70 (s, 3H), 1.30 (t, 3H), 1.20 (d, 6H).



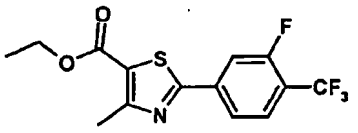
Intermediate 14:

Intermediate **7** was reacted as described in general procedure 3 to afford the title compound as an yellow solid (74%). ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 2H), 8.05 (d, 2H), 4.30 (q, 2H), 2.70 (s, 3H), 1.30 (t, 3H).



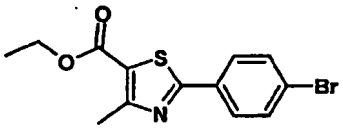
Intermediate 15:

Intermediate **8** was reacted as described in general procedure 3 to afford the title compound as an pale yellow solid (77%). ^{1}H NMR ($CDCl_3$): δ 8.0 (d, 1H), 7.70 (dd, 1H), 7.40 (d, 1H), 4.30 (q, 2H), 2.70 (s, 3H), 1.3 (s, 3H).



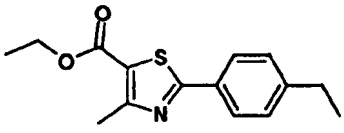
Intermediate 16:

Intermediate **9** was reacted as described in general procedure 3 to afford the title compound as an off-white solid (40%). ^{1}H NMR (DMSO-d_6): δ 7.95 (m, 3H), 4.30 (q, 2H), 2.65 (s, 3H), 1.3 (s, 3H).



Intermediate 17:

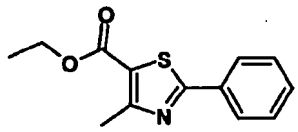
Intermediate **10** was reacted as described in general procedure 3 to afford the title compound as an off-white solid (61%). ^{1}H NMR ($CDCl_3$): δ 7.70 (d, 2H), 7.55 (d, 2H), 4.25 (q, 2H), 2.70 (s, 3H), 1.30 (s, 3H).



Intermediate 18:

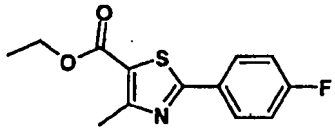
Intermediate **11** was reacted as described in general procedure 3 to afford the title compound as a pale green solid (35%). ^{1}H NMR ($CDCl_3$): δ 7.70

(d, 2H), 7.15 (d, 2H), 4.15 (q, 2H), 2.50 (s, 3H), 2.50 (q, 2H), 1.15 (t, 3H), 1.05 (t, 3H).



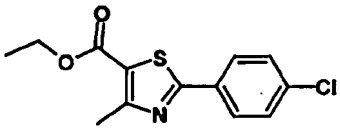
Intermediate 19:

The thiobenzamide (Aldrich) was reacted as described in general procedure 3 to afford the title compound as an off-white solid (28%). ^{1}H NMR ($CDCl_3$): δ 8.35 (d, 2H), 7.60 (m, 3H), 4.45 (q, 2H), 3.05 (s, 3H), 1.30 (t, 3H).



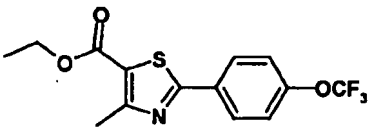
Intermediate 20:

The 4-fluorothiobenzamide (Maybridge) was reacted as described in general procedure 3 to afford the title compound as an off-white solid (100%). ^{1}H NMR ($CDCl_3$): δ 7.75 (dd, 2H), 6.95 (t, 2H), 4.15 (q, 2H), 2.60 (s, 3H), 1.20 (t, 3H).



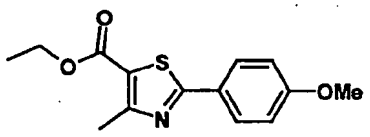
Intermediate 21:

The 4-chlorothiobenzamide (Lancaster) was reacted as described in general procedure 3 to afford the title compound as an pale orange solid (54%). ^{1}H NMR ($CDCl_3$): δ 7.60 (d, 2H), 7.10 (d, 2H), 4.15 (q, 2H), 2.55 (s, 3H), 1.20 (t, 3H).



Intermediate 22:

The 4-trifluoromethoxythiobenzamide (Interchim) was reacted as described in general procedure 3 to afford the title compound as an off-white solid (100%). ^{1}H NMR ($CDCl_3$): δ 7.90 (d, 2H), 7.15 (d, 2H), 4.25 (q, 2H), 2.65 (s, 3H), 1.30 (t, 3H).

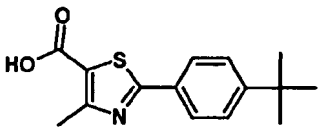


Intermediate 23:

The 4-methoxythiobenzamide (Lancaster) was reacted as described in general procedure 3 to afford the title compound as an off-white solid (52%). ^{1}H NMR (DMSO-d_6): δ 7.8 (d, 2H), 6.95 (d, 2H), 4.15 (q, 2H), 3.70 (s, 3H), 2.50 (s, 3H), 1.15 (t, 3H).

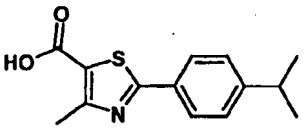
General procedure 4 for the preparation of 2-substituted phenyl-4-methyl-1,3-thiazole-5-caboxylic acids

To a solution of the substituted thiazole ester (1 mmol) in EtOH (100 mL) was added (1.5 equiv.) NaOH (1N) and the mixture heated to 40°C overnight. The reaction is cooled to room temperature and the solution acidified with HCl (1N). The precipitate is collected washed with H_2O and dried under vaccum to afford the final product.



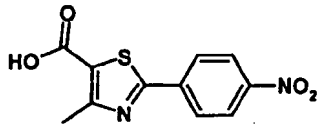
Intermediate 24:

Intermediate **12** was reacted as described in general procedure 4 to afford the title compound as an off-white solid (64%). ^{1}H NMR ($CDCl_3$): δ 7.70 (d, 2H), 7.30 (d, 2H), 2.60 (t, 3H), 1.15 (s, 9H).



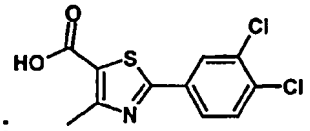
Intermediate 25:

Intermediate **13** was reacted as described in general procedure 4 to afford the title compound as an off-white solid (100%). ^{1}H NMR ($CDCl_3$): δ 7.75 (d, 2H), 7.15 (d, 2H), 2.85 (st, 1H), 2.65 (s, 3H), 1.15 (d, 6H).



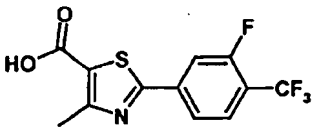
Intermediate 26:

Intermediate **14** was reacted as described in general procedure 4 to afford the title compound as a beige solid (99%). ^{1}H NMR (DMSO-d_6): δ 8.15 (d, 2H), 8.05 (d, 2H), 2.50 (s, 3H).



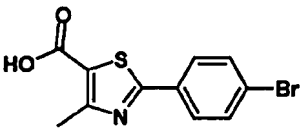
Intermediate 27:

Intermediate **15** was reacted as described in general procedure 4 to afford the title compound as an off-white solid (91%). ^{1}H NMR (DMSO-d_6): δ 8.35 (d, 1H), 8.05 (dd, 1H), 7.90 (d, 1H), 2.80 (s, 3H).



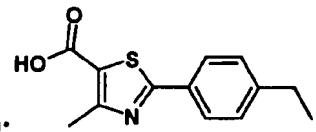
Intermediate 28:

Intermediate **16** was reacted as described in general procedure 4 to afford the title compound as an off-white solid (82%). ^{1}H NMR (DMSO-d_6): δ 8.05 (m, 3H), 2.75 (s, 3H).



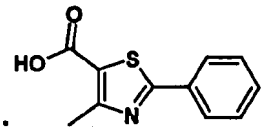
Intermediate 29:

Intermediate **17** was reacted as described in general procedure 4 to afford the title compound as an off-white solid (87%). ^{1}H NMR (DMSO-d_6): δ 7.70 (d, 2H), 7.45 (d, 2H), 2.45 (s, 3H).



Intermediate 30:

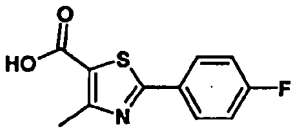
Intermediate **18** was reacted as described in general procedure 4 to afford the title compound as a pale green solid (79%). ^{1}H NMR (DMSO-d_6): δ 8.05 (d, 2H), 7.50 (d, 2H), 2.75 (q, 2H), 2.75 (s, 3H), 1.30 (t, 3H).



Intermediate 31:

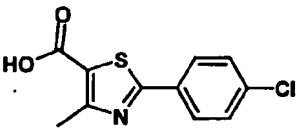
Intermediate **19** was reacted as described in general procedure 4 to afford the title compound as an off-white solid (93%).

Mp 215°C



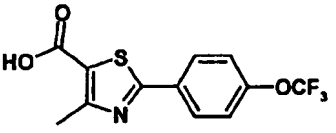
Intermediate 32:

Intermediate **20** was reacted as described in general procedure 4 to afford the title compound as an off-white solid (85%). ^{1}H NMR (DMSO-d_6): δ 8.0 (dd, 2H), 7.30 (t, 2H), 2.60 (s, 3H).



Intermediate 33:

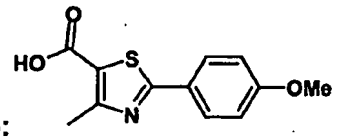
Intermediate **21** was reacted as described in general procedure 4 to afford the title compound as an pale orange solid (92%). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 2H), 7.55 (d, 2H), 2.60 (s, 3H).



Intermediate 34:

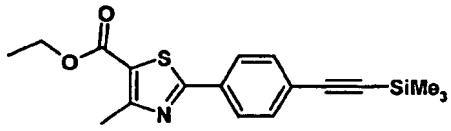
Intermediate **22** was reacted as described in general procedure 4 to afford the title compound as an off-white solid (66%).

MS m/z 304 (M+1)



Intermediate 35:

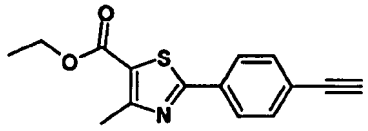
Intermediate **23** was reacted as described in general procedure 3 to afford the title compound as an off-white solid (98%). ^{1}H NMR (DMSO-d_6): δ 7.95 (d, 2H), 7.10 (d, 2H), 3.90 (s, 3H), 2.70 (s, 3H).



Intermediate 36:

Intermediate **17** (1 mmol) was diluted in a mixture of MeCN/dioxane (100mL) then CuI (0.05 equiv.) and 1,1,3,3-tertamethylguanidine (10 equiv.) was added and the reaction stirred 15min under a N_2 atmosphere. The reaction purged under vaccum and then trimethylsilylacetylene (1.1 equiv.) and $Pd(PPh_3)_2Cl_2$ (0.1 equiv.) added and the reaction stirred at 80°C for 2h. The solvent evaporated, the residue dissolved in CH_2Cl_2, washed with sat. NH_4Cl, then NH_4OH and finally brine. The organic layer dried over Na_2SO_4, filtered and evaporated. The crude product was chromatographed eluting with CH_2Cl_2 to afford the title compound as a beige solid (100%).

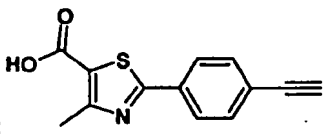
MS m/z 344 (M+1)



Intermediate 37:

To intermediate **36** (1 mmol) in THF was added Bu_4NF and the reaction stirred at rt for 2h. The THF was evaporated, the residue dissolved in CH_2Cl_2, washed with sat. NH_4Cl, then NH_4OH and finally brine. The organic layer dried over Na_2SO_4, filtered and evaporated. The crude product was chromatographed eluting with CH_2Cl_2 to afford the title compound as white solid (44%).

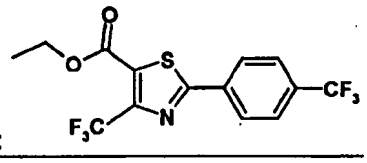
MS m/z 272 (M+1)



Intermediate 38:

Intermediate **37** was reacted as described in general procedure 4 to afford the title compound as a pale yellow solid (79%).

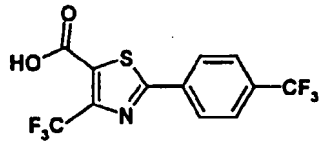
MS m/z 244 (M+1)



Intermediate 39:

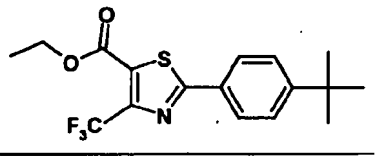
To the 4-trifluoromethylthiobenzamide (1equiv., Lancaster) in DMF (150mL) was added ethyl 2-chloro-4,4,4-trifluoroacetoacetate (1.5 equiv., Lancaster) and the reaction stirred at 100°C for 18h. The reaction is cooled, concentrated and the residue chromatographed eluting with CH_2Cl_2. The yellow oil that is collected is titrated with hexane to afford the title compound as a white solid (13%).

MS m/z 369



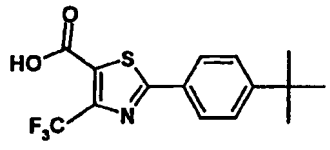
Intermediate 40:

Intermediate **39** was reacted as described in general procedure 4 to afford the title compound as a white solid (94%). ^1H NMR (DMSO-d_6): δ 8.1 (d, 2H), 7.7 (d, 2H).



Intermediate 41:

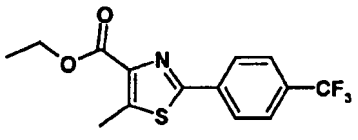
To intermediate **5** (1equiv.) in EtOH (25mL) was added ethyl 2-chloro-4,4,4-trifluoroacetoacetate (1 equiv., Lancaster) and the reaction stirred at reflux for 91h. The reaction is cooled, concentrated, the residue dissolved in pentane and filtered. The solvent removed under vaccum to afford the title compound as a brown oil containing 2 compounds which was used without further purification.



Intermediate 42:

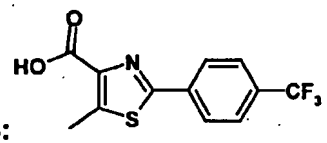
Intermediate **41** was reacted as described in general procedure 4 to afford the title compound as a mixture of 2 compounds. The mixture was chromatographed with cyclohexane/ethyl acetate (7/3) to recover the impurity then with CH_2Cl_2/MeOH (98/2) to recover the title compound as a white solid (9.7%).

MS m/z 329 (M+1)



Intermediate 43:

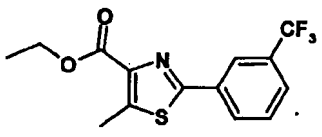
To the 4-trifluoromethylthiobenzamide (1 equiv., Lancaster) in EtOH (100mL) was added the ethyl 3-bromo-2-oxobutyrate (1.1 equiv.) and the reaction stirred at reflux for 18h. The reaction cooled to rt, concentrated and the residue dissolved in CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ followed by H_2O, dried over Na_2HCO_4, filtered and the solvent evaporated to dryness; The crude product was chromatographed eluting with CH_2Cl_2 to afford the title compound as a white solid (60%).



Intermediate 44:

Intermediate **43** was reacted as described in general procedure 4 to afford the title compound as a white solid (74%).

MS m/z 287

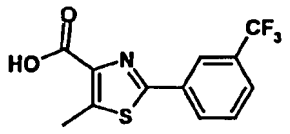


Intermediate 45:

To the 3-trifluoromethylthiobenzamide (1 equiv., Lancaster) in EtOH (100mL) was added the ethyl 3-bromo-2-oxobutyrate (1.1 equiv.) and the

reaction stirred at reflux for 18h. The reaction cooled to rt, concentrated and the residue dissolved in CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ followed by H_2O, dried over Na_2HCO_4, filtered and the solvent evaporated to dryness; The crude product was chromatographed eluting with CH_2Cl_2 to afford the title compound as a yellow oil (81%).

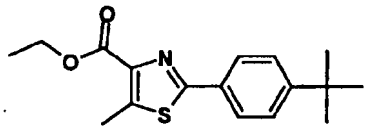
MS m/z 315



Intermediate 46:

Intermediate **45** was reacted as described in general procedure 3 to afford the title compound as a white solid (92%).

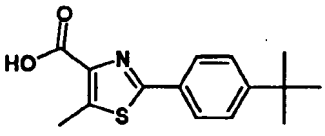
MS m/z 288 (M+1)



Intermediate 47:

Intermediate **5** (1 equiv.) in EtOH (100mL) was added the ethyl 3-bromo-2-oxobutyrate (1.1 equiv.) and the reaction stirred at reflux for 18h. The reaction cooled to rt, concentrated and the residue dissolved in CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ followed by H_2O, dried over Na_2HCO_4, filtered and the solvent evaporated to dryness; The crude product was chromatographed eluting with CH_2Cl_2 to afford the title compound as a pale yellow solid (56%).

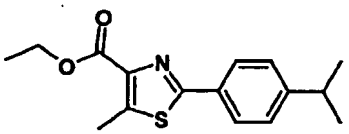
Mp 108°C



Intermediate 48:

Intermediate **47** was reacted as described in general procedure 4 to afford the title compound as a pale yellow solid (99%).

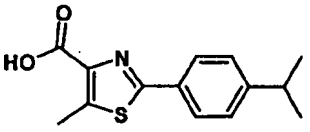
Mp 155°C



Intermediate 49:

Intermediate **6** (1 equiv.) in EtOH (100mL) was added the ethyl 3-bromo-2-oxobutyrate (1.1 equiv.) and the reaction stirred at reflux for 18h. The reaction cooled to rt, concentrated and the residue dissolved in CH_2Cl_2. The organic layer was washed with sat. $NaHCO_3$ followed by H_2O, dried over Na_2HCO_4, filtered and the solvent evaporated to dryness; The crude product was chromatographed eluting with CH_2Cl_2 to afford the title compound as a yellow oil (48%).

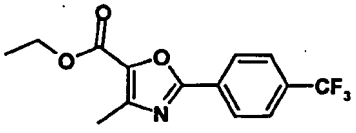
MS m/z 289



Intermediate 50:

Intermediate **49** was reacted as described in general procedure 4 to afford the title compound as a white solid (73%).

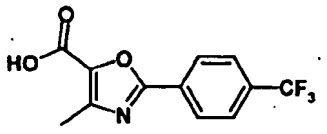
MS m/z 262 (M+1)



Intermediate 51:

To 4-(trifluoromethyl)benzamide (1 equiv.) in toluene (150mL) was added droppwise the methyl 3-bromo-2-oxobutyrate (1 equiv.) and the reaction stirred at reflux for 20h. The reaction was diluted with EtOAc (100 mL) and succesively washed with: NaOH (1N), HCl (1N) and water (3 x 100 mL), dried, filtered and evaporated to a syrup. The resulting mixture was purified by flash column chromatography [CH_2Cl_2 then CH_2Cl_2/MeOH (99.5:0.5)] to afford the title compound as a white solid (9%).

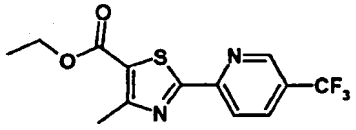
MS m/z 285



Intermediate 52:

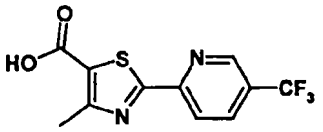
Intermediate **51** was reacted as described in general procedure 4 to afford the title compound as a white solid (86%).

Mp189



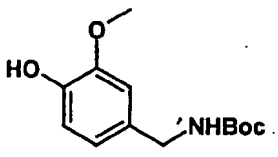
Intermediate 53:

(4-trifluoromethyl-2-pyridyl)thioamide (Lancaster) was reacted as described in general procedure 3 to afford the title compound as a white solid (48%).



Intermediate 54:

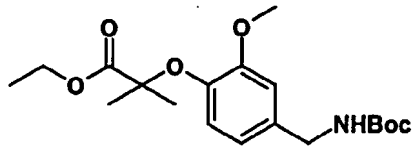
Intermediate **53** was reacted as described in general procedure 4 to afford the title compound as a grey solid (84%). ^{1}H NMR (DMSO-d_6): δ 9.13 (d, 1H), 8.43 (dd, 1H), 8.35 (d, 1H), 2.75 (s, 3H).



Intermediate 55:

To 4-hydroxy-3-methoxybenzylamine hydrochloride (1 equiv., Aldrich) in CH_2Cl_2 (300mL) at 0°C was added Et_3N (3 equiv.). Boc anhydride (0.95 equiv.) in CH_2Cl_2 (50mL) was added dropwise. The reaction was allowed to warm to rt and stirring continued for 18h. The reaction was then poured into NaOH (1N) and the mixture extracted with NaOH (3 x 50mL). The aqueous phases combined, acidified with HCl (1N) and extracted with CH_2Cl_2 (3 x 100mL). The oranic layers washed with H_2O, dried over Na_2SO_4, filtered and the solvent removed under vaccum to afford the title compound as a clear oil (97%). ^{1}H

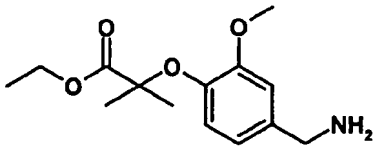
NMR ($CDCl_3$): δ 6.75 (m, 3H), 5.55 (bs, 1H), 4.75 (bs, 1H), 4.15 (d, 2H), 3.80 (s, 3H), 1.40 (s, 9H).



Intermediate 56:

To intermediate **55** (1 equiv.) in DMSO (100mL) was added K_2CO_3 (3 equiv.) and ethyl 2-bromo-2-methylproprionate (1.3 equiv.). The reaction was stirred while heating at 100°C for 3h. The reaction was poured onto ice and extracted with CH_2Cl_2 (3 x 150mL). The combined organic layers were washed with NaOH (1N), then H_2O and dried over Na_2SO_4. The solution filtered, evaporated to dryness and the crude product cristallized from hot hexane to afford the title compound as a brown solid (63%).

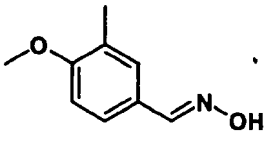
Mp 107-109°C



Intermediate 57:

To intermediate **56** (1 equiv.) in CH_2Cl_2 (10mL) at rt was added droppwise CF_3COOH (7 equiv.) and the reaction stirred at rt for 18h. The reaction was evaporated to dryness, treated with a sat. K_2CO_3 solution and extracted with CH_2Cl_2 (3 x 150mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to afford the title compound as an oil (100%).

MS m/z 267

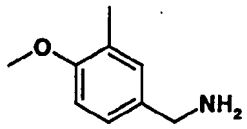


Intermediate 58:

To 4-methoxy-3-methylbenzalehyde (1 equiv., Acros) in EtOH (150mL) at rt was added H_2NOH,HCl (1.6 equiv.), (3equiv.) NaOAc in 150mL H_2O and the reaction stirred for 2h. The EtOH was evaporated, and the residue extracted

with CH_2Cl_2 (3 x 50mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated to dryness to afford the title compound as a white solid (93%).

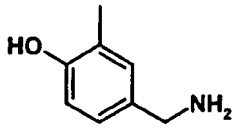
Mp 71-73°C



Intermediate 59:

To intermediate **58** (1 equiv.) in MeOH (200mL) at rt was added $[MeCO_2]NH_4$ (6 equiv.), Pd/C (0.01 equiv.) and molecular sieves. The reaction was then heated to reflux for 18h. The reaction was filtered through celite, evaporated to dryness and treated with HCl (1N). The aqueous layer was washed with CH_2Cl_2 , filtered, basified to pH >14 and extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4, filtered and evaporated to dryness to afford the title compound as an oil (46%).

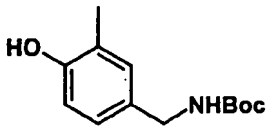
MS m/z 151



Intermediate 60:

Intermediate **59** (1 equiv.) in excess 40% HBr/H_2O (Aldrich) was refluxed for 18h. The reaction was then evaporated to dryness to afford the title compound hydrobromide salt as a grey solid (97%).

Mp 235-237°C

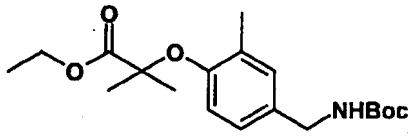


Intermediate 61:

To Intermediate **60** (1 equiv.) in CH_2Cl_2 (300mL) at 0°C was added Et_3N (3 equiv.). Boc anhydride (0.95 equiv.) in CH_2Cl_2 (50mL) was added dropwise. The reaction was allowed to warm to rt and stirring continued for 18h. HCl (1N) was added and the reaction extracted with CH_2Cl_2 (3 x 100mL). The organic

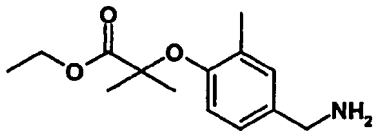
layers washed with H_2O, dried over Na_2SO_4, filtered and the solvent removed under vaccum to afford the title compound as a white solid (96%).

Mp 105-107°C



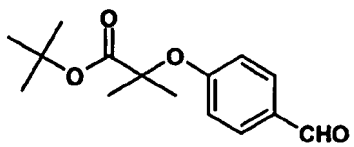
Intermediate 62:

To intermediate **61** (1 equiv.) in DMF (150mL) was added K_2CO_3 (3 equiv.) and the reaction heated to 70°C. Ethyl 2-bromo-2-methylproprionate (1.3 equiv.) was added droppwise and the reaction was stirred for 72h at 70°C. The reaction was poured onto ice and extracted with CH_2Cl_2 (3 x 150mL). The combined organic layers were washed with NaOH (0.5N), then H_2O and dried over Na_2SO_4. The solution filtered, evaporated to dryness to afford the title compound as an oil (69%). ^1H NMR ($CDCl_3$): δ 7.05 (d, 1H), 6.90 (dd, 1H), 6.60 (d, 1H), 4.80 (bs, 1H), 4.25 (q, 2H), 4.20 (d, 2H), 2.20 (s, 3H), 1.60 (s, 6H), 1.45 (s, 9H), 1.25 (t, 3H).



Intermediate 63:

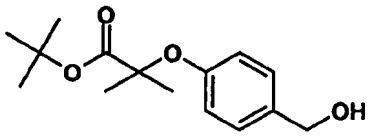
To intermediate **62** (1 equiv.) in CH_2Cl_2 (10mL) at rt was added dropwise CF_3COOH (7 equiv.) and the reaction stirred at rt for 18h. The reaction was evaporated to dryness, treated with a sat. K_2CO_3 solution and extracted with CH_2Cl_2 (3 x 150mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to afford the title compound as an oil (82%). ^1H NMR ($CDCl_3$): δ 7.00 (d, 1H), 6.90 (dd, 1H), 6.55 (d, 1H), 4.20 (q, 2H), 3.70 (s, 2H), 2.15 (s, 3H), 1.85 (bs, 2H), 1.50 (s, 6H), 1.20 (t, 3H).



Intermediate 64:

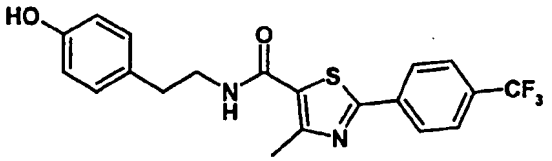
To 4-hydroxybenzaldehyde (1 equiv.) in DMF (150mL) was added NaH (1.5 equiv.) and the reaction stirred at 80°C for 30min. Ethyl 2-bromo-2-

methylproprionate (1.2 equiv.) was added dropwise and the reaction was stirred for 24h at 80°C. The reaction was evaporated to dryness, the residue treated with NaOH and extracted with CH_2Cl_2 (5 x 100mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated to to afford crude intermediate **64**. After chromatography eluting with CH_2Cl_2/MeOH (98:2) the title compound was obtained as an oil (20%). ^1H NMR ($CDCl_3$): δ 9.80 (s, 1H), 7.75 (d, 2H), 6.80 (d, 2H), 1.55 (s, 6H), 1.3 (s, 9H).



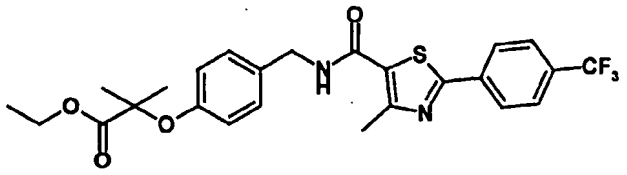
Intermediate 65:

To intermediate **64** (1 equiv.) in MeOH (50mL) at rt was added $NaBH_4$ (1 equiv.) and the reaction stirred at rt while it was followed by tlc [CH_2Cl_2/MeOH (98:2); *Rf* = 0.45]. When all the starting material had disappeared, the solvent was evaporated to dryness, the residue treated with H_2O and extracted with CH_2Cl_2 (3 x 50mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness to afford the title compound as a semi-solid (100%). ^1H NMR ($CDCl_3$): δ 7.20 (d, 2H), 6.80 (d, 2H), 4.55 (s, 2H), 1.50 (s, 6H), 1.35 (s, 9H).



Intermediate 66:

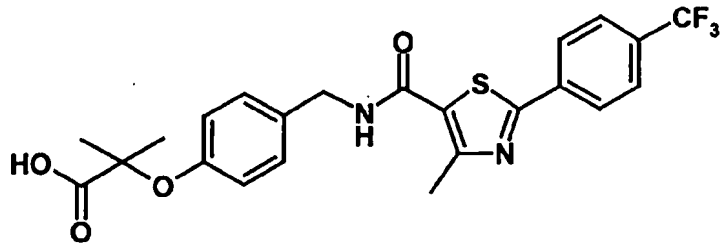
To the 4-hydroxyphenethyl amine (1 equiv.) in DMF (75mL) at rt was added HOBT (1.1 equiv.), EDC (1.1 equiv.) and Et_3N (1.5 equiv.). To the mixture was added dropwise intermediate **3** in DMF and the reaction was stirred at rt for 18h. The reaction was evaporated to dryness, treated with a HCl (1N) and extracted with EtOAc (3 x 150mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The crude intermediate **66** was chromatogaphed eluting with CH_2Cl_2/MeOH (9:1) to afford the title compound as a white solid (64%). ^1H NMR ($CDCl_3$): δ 9.2 (s, 1H), 8.40 (t, 3H), 8.10 (d, 2H), 7.85 (d, 2H), 7.05 (d, 2H), 6.70 (d, 2H), 3.40 (m, 2H), 2.70 (m, 2H), 2.60 (s, 3H).



Example 1:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

To intermediate **4** (710mg, 1.81 mmol) in DMF (50mL) was added the K_2CO_3 (275mg, 1.99 mmol) followed by the ethyl 2-bromo-2-methylpropanoate (280µL, 1.91 mmol; Aldrich) and the reaction heated to 80°C. After 18h, the reaction was cooled to rt and the solvent removed *in vacuo*. The residue was treated with water (200 mL), extracted 3 x 50mL CH_2Cl_2, dried over Na_2SO_4, filtered and the solvent removed under vacuum. The residue was chromatographed (CH_2Cl_2/MeOH: 99/1) to afford 680mg (77%) of example **1** as a clear oil. ^1H NMR($CDCl_3$): δ 7.95 (d, 2H), 7.60 (d, 2H), 7.15 (d, 2H), 6.75 (d, 2H), 6.05 (t, 1H), 4.45 (d, 2H), 4.15 (q, 2H), 2.65 (s, 3H), 1.50 (s, 6H), 1.20 (t, 3H).

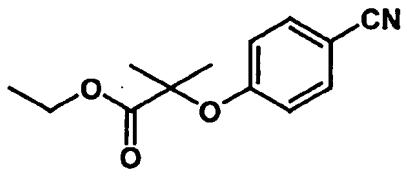


Example 2:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

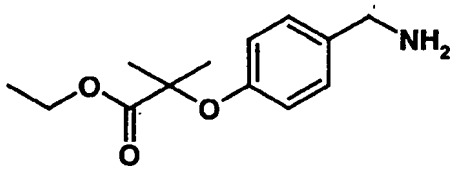
To Example 1 (680mg, 1.39 mmol) in MeOH was added 1N NaOH (1.6 mL, 1.6 mmol) and the reaction stirred at 60°C. After 18h, the reaction cooled to rt and the solvent evaporated. The residue was treated with 1N HCl, extracted 3 x 20 mL THF and the solvent removed under vacuum. 500mg (75%). The title compound was precipitated as a white solid from a minimum volume of CH_2Cl_2 and pentane. mp: changes form between 60-70°C; LC/MS (m/z): 477.22 (100%, AP-), 479.12 (100%, AP+); anal. $C_{23}H_{21}F_3N_2O_4S$: C 5.71 (57.73), H 4.56 (4.42), N 5.77 (5.85), S 6.15 (6.70).

An improved synthesis of 2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]-propionic acid is:



Intermediate 67:

To a solution of 212.8 g (1.79 moles) of para hydroxybenzonitrile in 1.7L of DMF (8 vol.) cooled to 15°C were added portionwise 121g (3.04 mol., 1.7 equiv.) of NaH dispersed in parafin (60%) in 35 minutes. After return to room temperature, the mixture was stirred for 30 minutes and 393mL (2.68 mol., 1.5 equiv.) of ethyl bromoisobutyrate were slowly added in 1 hour. During the addition, the inert temperature was maintained below 25°C by cooling because a slightly exothermic effect occurred. The mixture was stirred overnight at room temperature and heated at 80°C for 2 hours. After cooling at a temperature below 20°C, the excess of sodium hydride was destroyed by the addition of 600 ml of 1N sodium hydroxide solution. The aqueous solution was extracted 3 times with 1L of ethyl ether. The combined organic layers were washed twice with 200 ml of 1N sodium hydroxide solution (to eliminate traces of the para hydroxybenzonitrile) and 500 ml of brine. After drying on magnesium sulphate, filtered and concentrated to dryness, the oily residue was decanted and 33.5 g of the parafin oil was removed (the upper layer). The 189.9 g of the oily residue was estimate to be mixed with 14.9 g of residual parafin oil. Crude intermediate **67** was used without further purification. The yield is estimated to be about 42% (about 175 g).

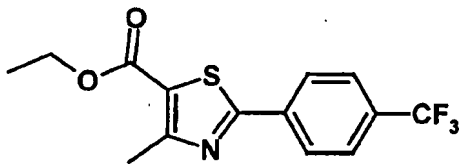


Intermediate 68:

In a hydrogenator of 1L, a mixture of 59.3 g of intermediate **67** (0.254 mol. (maximum), 43.6 ml (0.762 mol., 3 equiv.) of glacial acetic acid and 6 g (10% w/w) of Pd/C 10% in 250 ml of ethyl alcohol was hydrogenated over 2 bars

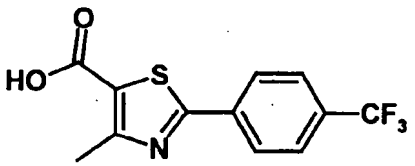
of hydrogen and at room temperature. The reaction stopped after 8 hours when 8.7 L of hydrogen were absorbed (theoretical volume: 11.4 L). After filtration of the catalyst, the solution was evaporated to dryness to give the acetic salt of intermediate **68** (oily residue). The residue was poured in 300 ml of water (pH = 5) and the aqueous layer was extracted twice with 200 ml of cyclohexane. During this operation, a gummy solid appeared which is left in the aqueous layer (probably a part of the acetic salt). After addition of 400 ml of ethyl acetate, the biphasic mixture was cooled to 15°C and treated with 500 ml of 1N NaOH solution (to pH = 12). After decantation, the aqueous layer was extracted twice with 400 ml of ethyl acetate. The combined organic layer was washed with 200 ml of brine.

After drying on magnesium sulphate, the organic layer was filtered and concentrated to dryness to give 35.5 g of crude intermediate **68** (yellow oil, yield = 58.9%) which were used in the next step without further purification (LC-MS purity = about 90%).



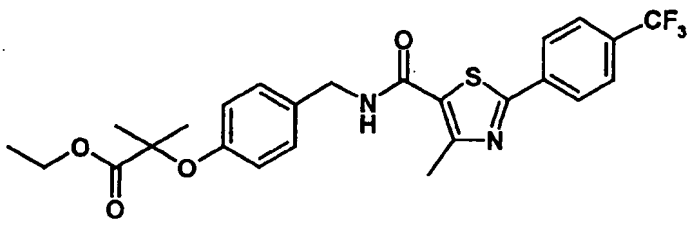
Intermediate 69:

To a suspension of 302.4 g (1.47 mol.) of 4-(trifluoromethyl)thiobenzamide in 1.5 L (5 vol.) of ethyl alcohol were added at room temperature in one time 203.8 ml (1 equiv.) of ethyl 2-chloroacetoacetate. The solution was refluxed for 24 hours. The reaction was follow up by tlc (CH_2Cl_2) and hplc. After completion of the reaction, the solvent was removed under reduce pressure. The solid material was stirred with 500 ml of cooled hexane for 30 minutes, filtered and washed twice with 150 ml of hexane. After drying, 352.9 g of crude intermediate **69** were obtained. A second crop of 25.7 g was obtained by concentration of hexane to 50 ml. The overall yield was 81.5% (378.6 g).



Intermediate 70:

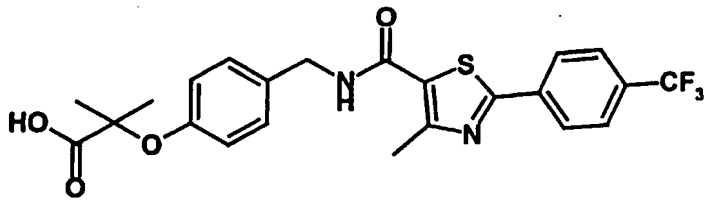
To a cooled solution of 378.6 g (1.2 mol.) of the intermediate **69** in 2 L (5 vol.) of ethyl alcohol were added 96.15 g (2 equiv.) of sodium hydroxide in 2 L of water. The solution was heated at 85°C for 1.5 hours. After evaporation of the ethyl alcohol, the aqueous solution was diluted with 2 L of water and acidified to pH = 1 with concentrated aqueous hydrochloric acid. The solid material was filtered, washed twice with 1 L of water and 1 L of dichloromethane. After drying in a vacuum oven, 267.2 g of an off-white powder were obtained. A second crop of 25.7 g was obtained by concentration of the dichloromethane and triturating with pentane. The overall yield was 85% (292.9 g).



Example 3:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

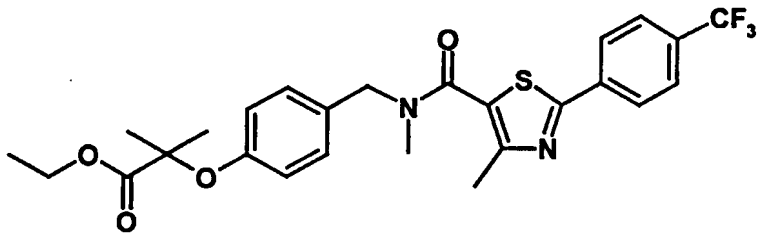
A suspension of 38.7 g (0.13 mol.) of crude intermediate **70** in 200 ml (5 vol.) of thionyl chloride was refluxed for 3 hours. After return to room temperature, the thionyl chloride was removed under reduce pressure, the residue was twice suspended in toluene (100 ml) and evaporated to dryness. The crude acid chloride obtained (off-white solid) was used without purification. To a solution of 35.5 g (1 equiv./LC-MS purity: 90%) of crude intermediate **68** and 20.62 ml (1.1 equiv.) of triethylamine in 350 ml of dichloromethane (10 vol.) maintained at 10°C, was added portionwise the acid chloride in 20 minutes. The mixture was then stirred at room temperature overnight. The reaction was quenched by addition of 200 ml of water and stirring for 5 minutes. The biphasic mixture was decanted and the aqueous layer extracted twice with 200 ml of dichloromethane. The whole organic layer was washed respectively with 200 ml of hydrochloric acid (1N), 200 ml of water, 200 ml of saturated aqueous sodium carbonate and 200 ml of brine. After drying on magnesium sulphate, filtration and concentration to dryness, the crude material was suspended in 200 ml of isopropyl ether, triturated, filtered and dried to give 47.6 g of example **3** (white powder, yield = 69.7%).



Example 4:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

To a solution of 230.8 g (0.46 mol.) of example **3** in 1.2 L (5 vol.) of tetrahydrofuran were added 480 ml (1.05 equiv.) of aqueous sodium (1N). The solution was stirred at reflux for 18 hours. After removal of THF under reduced pressure, 500 ml of 1N NaOH and 100 ml of methyl alcohol were added. The aqueous layer was extracted twice with 400 ml of dichloromethane and acidified to pH = 1 with concentrated aqueous hydrochloric acid. The oily residue was extracted with dichloromethane (3 x 400 ml). The whole organic layer was washed with 600 ml of brine. After drying on magnesium sulphate, filtration and concentration to dryness, the oily residue was organised with 500 ml of pentane, filtered, washed twice with 250 ml of pentane to give after drying 207.2 g of crude example **4** (white powder). The solid material was dissolved in 310 ml (1.5 vol.) of refluxed toluene. After filtration of the hot solution and return to room temperature, the crystallised material was filtered, washed twice with 200 ml of toluene and dried in vacuum oven to give 196.3 g of white powder of example **4** (yield = 90 %), mp = 130-131°C, tlc (CH_2Cl_2/MeOH = 9/1): monospot, hplc analysis: 99.5% (detection at 310 nm).



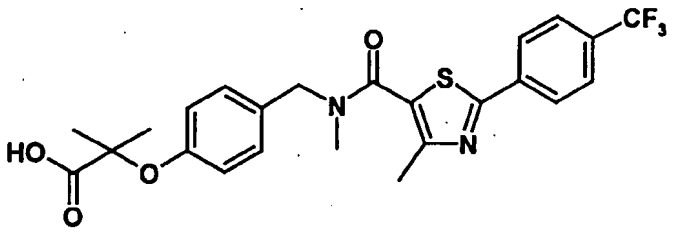
Example 5:

***N*-methyl-2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester**

To a solution of example **4** (600 mg, 1.2 mmol.) in 50 mL of DMF was added 32 mg (1.1 equiv.) of NaH and the mixture stirred at 40°C for 30min. 85

µL (1.1 equiv.) of MeI was then added and the reaction as stirred at 40°C for 18h. After removal of DMF under reduced pressure, the residue was washed with H_2O and extracted with Et_2O (3 x 50 mL). The organic layer combined and dried over Na_2SO_4, filtered, evaporated to dryness and chromatographed with 100% CH_2Cl_2 then 99:1 CH_2Cl_2 / MeOH to afford 300mg of example **5** as a clear oil (yield = 49%).

MS m/z 521 (M+1)



Example 6:

***N*-methyl-2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid**

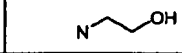
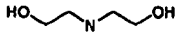
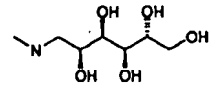
To a solution of example **5** (300 mg, 0.6 mmol) in 50 mL of EtOH was added 692 µL (1.2 equiv.) of NaOH (1N) and the mixture stirred at 60°C for 18h. After removal of EtOH under reduced pressure, the residue was treated with HCl and the solid collected, dried under vaccum and recrystallized from iPr_2O to afford 230mg of example **6** as a white solid (yield = 49%).

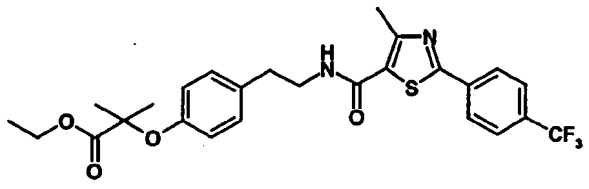
MS m/z 493 (M+1)

General proceedure 5 for the preparation of salts of 2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)-amino]methyl}phenoxy]propionic acid

At room temperature, to a solution of 500 mg of example **2** in 25 ml of acetonitrile was added 1 equivalent of the base*. After stirring for 3 or 24 hours*, the mixture was filtered and the solid material was washed with pentane and dried in a vacuum oven*. (*See table 1 of results below)

Table 1:

	Base	Quantity Base	Stirring Time	Amounts of salt	Yield
Example 5	NaOH (solution 1N)	1.05 ml	24h	0.37 g	71%
Example 6		58 µl	3h	0.38 g	68%
Example 7		100.2 µl	3h	0.55 g	90%
Example 8		0.204 g	24h	0.69 g	98%



Example 9:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid ethyl ester

To intermediate **66** (1 equiv.) in DMF (150mL) was added K_2CO_3 (1.2 equiv.), ethyl 2-bromo-2-methylpropionate (1.1 equiv.) and the reaction stirred at 80°C for 18h. The reaction was evaporated to dryness, the residue treated with NaOH (1N) and extracted with EtOAc (4 x 50mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated to to afford crude example **9**. After chromatography eluting with CH_2Cl_2/MeOH (95:5) the title compound was obtained as a white solid (86%). ^1H NMR ($CDCl_3$): δ 7.95 (d, 2H), 7.6 (d, 2H), 7.05 (d, 2H), 6.75 (d, 2H), 5.70 (t, 1H), 4.20 (q, 2H), 3.60 (m, 2H), 2.80 (m, 2H), 2.75 (s, 3H), 1.50 (s, 6H), 1.20 (t, 3H).

General procedure 6 for the peptide coupling reaction between intermediates of type A and B

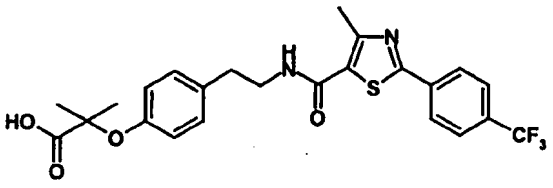
To intermediate **B** (1 equiv.) in CH_2Cl_2 (75mL) at rt was added HOBT (1.1 equiv.), EDC (1.1 equiv.) and Et_3N (3 equiv.). To the mixture was added intermediate **A** and the reaction was stirred at rt for 18h. The reaction was washed with HCl (1N), NaOH (1N) and 2 x H_2O. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The crude compound was chromatogaphed or crystallized as necessary to afford the final product.

General procedure 7 for the alkylation reaction between intermediates of type A and C

To intermediate **B** (1 equiv.) in toluene (25mL) was added $SOCl_2$ and the reaction heated at 80°C for 18h. The reaction evaporated to dryness to afford the crude intermediate **C** which was redissolved in 10mL toluene and re-evaporated to dryness. To intermediate **A** and Et_3N (3 equiv.) in CH_2Cl_2 (50mL) at rt was added intermediate **C** (1 equiv.) in CH_2Cl_2 and the reaction was stirred at rt for 3h. The reaction was washed with HCl (1N), NaOH (1N) and H_2O. The organic layer was dried over Na_2SO_4, filtered and evaporated to dryness. The crude compound was chromatogaphed or recrystallized as necessary to afford the final product.

General procedure 8 for the hydrolysis of the ethyl esters

To a solution of the ethyl ester (1 mmol) in MeOH (50 mL) was added (3 equiv.) NaOH (1N) and the mixture heated to 60°C overnight. The reaction is cooled to room temperature and the solution acidified with HCl (1N) and extracted with CH_2Cl_2 (3 x 25mL). The combined organic layers washed with H_2O, dried over Na_2SO_4, filtered and evaporated to dryness. The solid was titrated with Et_2O, collected and dried under vaccum to afford the final product.

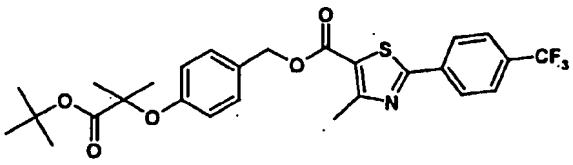


Example 10:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid

Example 9 was reacted as described in general procedure 8 to afford the title compound as a white solid (74%).

MS m/z 493 (M+1)

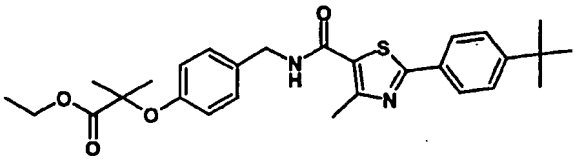


Example 11:

4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-carboxylic acid 4-(1-tertbutyloxycarbonyl-1-methylethoxy) benzyl ester

To intermediate **65** (1 equiv.) in DMF (150mL) was added intermediate **3** (1 equiv.), DMAP (0.1 equiv.) and DIC (1.1 equiv.). The reaction was stirred at rt while it was followed by tlc [CH_2Cl_2/MeOH (98:2); *Rf* = 0.85]. The reaction was evaporated to dryness, the residue treated with NaOH (1N) and extracted with CH_2Cl_2 (5 x 100mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent evaporated to to afford crude example **11**. After chromatography eluting with CH_2Cl_2/MeOH (80:20) the title compound was obtained as a clear oil that solidified upon sitting (44%).

Mp 72°C

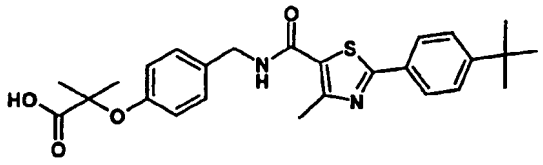


Example 12:

2-methyl-2-[4-{[(4-methyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **24** and Intermediate **68** were reacted as described in general procedure 6 to afford the title compound as a white solid (72%). Chromatographed: CH_2Cl_2, then CH_2Cl_2/MeOH (99:1), then CH_2Cl_2/MeOH (98:2)

MS m/z 495 (M+1)

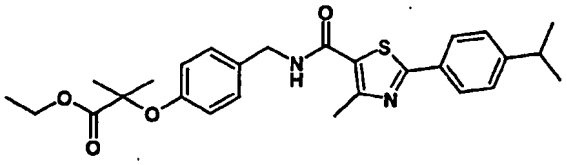


Example 13:

2-methyl-2-[4-{[(4-methyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **12** was reacted as described in general procedure 8 to afford the title compound as a white solid (22%).

MS m/z 466 (M+1)

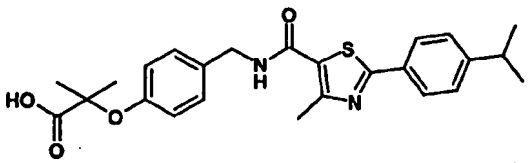


Example 14:

2-methyl-2-[4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **25** and Intermediate **68** were reacted as described in general procedure 6 to afford the title compound as a white solid (54%). Chromatographed: CH_2Cl_2, then CH_2Cl_2/MeOH (99:1), then CH_2Cl_2/MeOH (98:2)

MS m/z 481 (M+1)

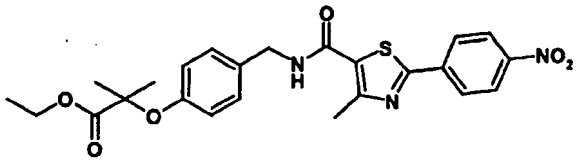


Example 15:

2-methyl-2-[4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **14** was reacted as described in general procedure 8 to afford the title compound as a white solid (100%).

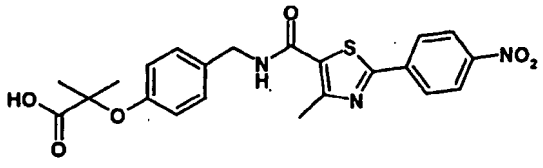
MS m/z 453 (M+1)



Example 16:

2-methyl-2-[4-{[(4-methyl-2-[4-nitrophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **26** and Intermediate **68** were reacted as described in general procedure 7 to afford the title compound as a brownish yellow oil (71%). Chromatographed: CH_2Cl_2/MeOH (99.5:0.5). ^1H NMR ($CDCl_3$): δ 8.15 (d, 2H), 7.95 (d, 2H), 7.15 (d, 2H), 6.75 (d, 2H), 6.15 (t, 1H), 4.45 (d, 2H), 4.15 (q, 2H), 2.65 (s, 3H), 1.50 (s, 6H), 1.15 (t, 3H).

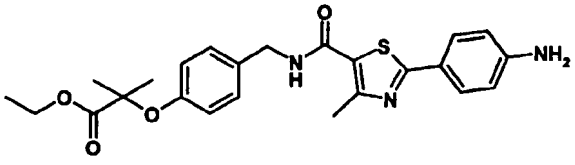


Example 17:

2-methyl-2-[4-{[(4-methyl-2-[4-nitrophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **16** was reacted as described in general procedure 8 to afford the title compound as a yellow solid (34%).

Mp 164°C

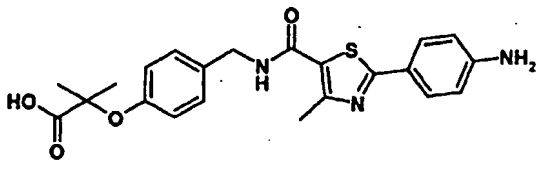


Example 18:

2-methyl-2-[4-{[(4-methyl-2-[4-aminophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

To intermediate **16** in EtOH (75mL) was added 10% Pd/C (0.01 equiv.). The reaction was degassed and place under an atmosphere of H_2 at rt for 18h. The reaction was filtered through celite and the solvent removed under vacuum to afford the title compound as a yellow oil (100%).

MS m/z 454 (M+1)

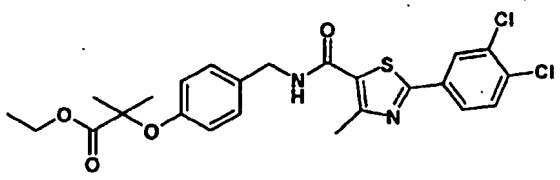


Example 19:

2-methyl-2-[4-{[(4-methyl-2-[4-aminophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **18** was reacted as described in general procedure 8 to afford the title compound as a yellow solid (80%).

MS m/z 426 (M+1)

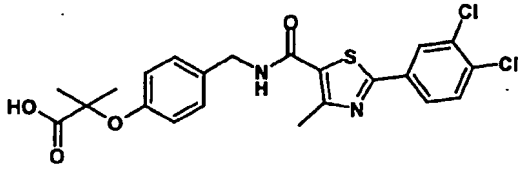


Example 20:

2-methyl-2-[4-{[(4-methyl-2-[3,4-dichlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **27** and Intermediate **68** were reacted as described in general procedure 7 to afford the title compound as a white solid (55%). Chromatographed: CH_2Cl_2, then CH_2Cl_2/MeOH (99.5:0.5).

MS m/z 507

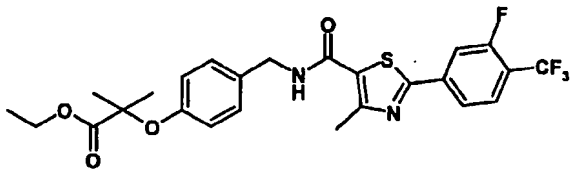


Example 21:

2-methyl-2-[4-{[(4-methyl-2-[3,4-dichlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **20** was reacted as described in general procedure 8 to afford the title compound as a white solid (84%).

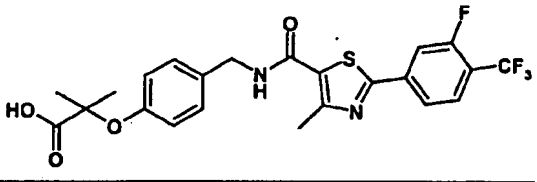
MS m/z 480 (M+1)



Example 22:

2-methyl-2-[4-{[(4-methyl-2-[3-fluoro-4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **28** and Intermediate **68** were reacted as described in general procedure 6 to afford the title compound as a clear oil (52%). Chromatographed: cyclohexane/EtOAc (9:1 to 7:3). ^{1}H NMR (DMSO-d_6): δ 8.90 (t, 1H), 8.00 (m, 3H), 7.25 (d, 2H), 6.75 (d, 2H), 4.40 (d, 2H), 4.15 (q, 2H), 2.65 (s, 3H), 1.55 (s, 6H), 1.15 (t, 3H).

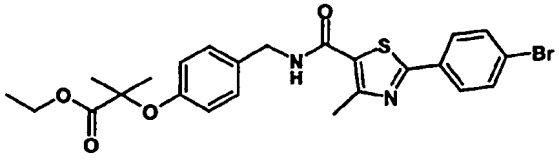


Example 23:

2-methyl-2-[4-{[(4-methyl-2-[3-fluoro-4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **22** was reacted as described in general procedure 8 to afford the title compound as a white solid (70%).

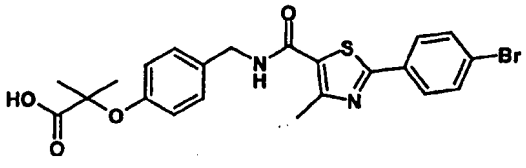
MS (AP-) m/z 495 (M-1)



Example 24:

2-methyl-2-[4-{[(4-methyl-2-[4-bromophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **29** and Intermediate **68** were reacted as described in general procedure 7 to afford the title compound as a white solid (52%). Chromatographed: CH_2Cl_2, then CH_2Cl_2/MeOH (99.5:0.5), then CH_2Cl_2/MeOH (99:1). ^{1}H NMR ($CDCl_3$): δ 7.55 (d, 2H), 7.35 (d, 2H), 7.05 (d, 2H), 6.65 (d, 2H), 6.25 (t, 1H), 4.35 (d, 2H), 4.10 (q, 2H), 2.55 (s, 3H), 1.45 (s, 6H), 1.10 (t, 3H).

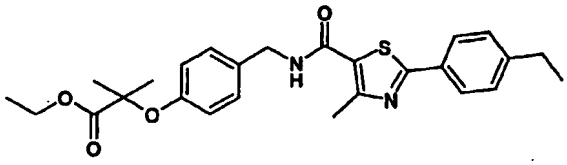


Example 25:

2-methyl-2-[4-{[(4-methyl-2-[4-bromophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **24** was reacted as described in general procedure 8 to afford the title compound as a white solid (90%).

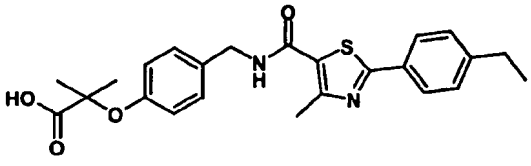
MS m/z 489



Example 26:

2-methyl-2-[4-{[(4-methyl-2-[4-ethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **30** and Intermediate **68** were reacted as described in general procedure 6 to afford the title compound as a clear oil (54%). Chromatographed: cyclohexane/EtOAc (8:2 to 6:4). ^{1}H NMR (DMSO-d_6): δ 8.55 (t, 1H), 7.65 (d, 2H), 7.10 (d, 2H), 7.00 (d, 2H), 6.55 (d, 2H), 4.15 (d, 2H), 3.95 (q, 2H), 2.45 (q, 2H), 2.40 (s, 3H), 1.30 (s, 6H), 1.00 (t, 3H), 0.95 (t, 3H).

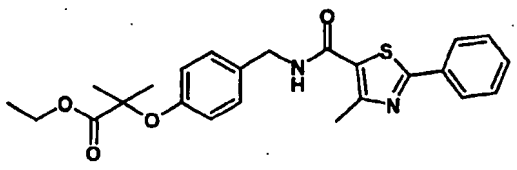


Example 27:

2-methyl-2-[4-{[(4-methyl-2-[4-ethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **26** was reacted as described in general procedure 8 to afford the title compound as a white solid (62%).

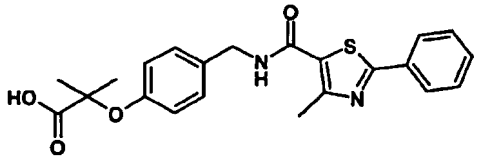
MS m/z 439 (M+1)



Example 28:

2-methyl-2-[4-{[(4-methyl-2-phenylthiazol-5-ylcarbonyl)amino]-methyl}phenoxy]propionic acid ethyl ester

Intermediate **31** and Intermediate **68** were reacted as described in general procedure 7 to afford the title compound as a clear oil (52%). ^{1}H NMR ($CDCl_3$): δ 7.85 (m, 2H), 7.35 (m, 3H), 7.15 (d, 2H), 6.75 (d, 2H), 6.00 (t, 1H), 4.50 (d, 2H), 4.15 (q, 2H), 2.65 (s, 3H),1.5 (s, 6H), 1.2 (t, 3H).

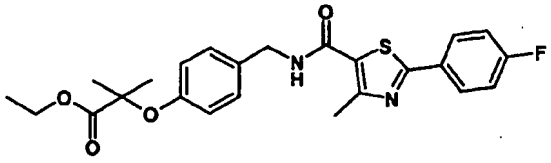


Example 29:

2-methyl-2-[4-{[(4-methyl-2-phenylthiazol-5-ylcarbonyl)amino]-methyl}phenoxy]propionic acid

Example **28** was reacted as described in general procedure 8 to afford the title compound as a white solid (46%).

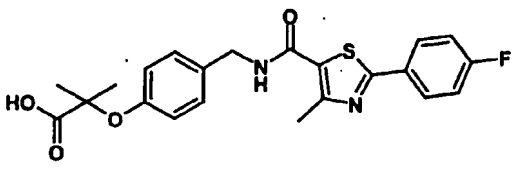
Mp 179°C



Example 30:

2-methyl-2-[4-{[(4-methyl-2-[4-fluorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **32** and Intermediate **68** were reacted as described in general procedure 7 to afford the title compound as a clear oil that solidified on standing (63%). Chromatographed: CH_2Cl_2, then CH_2Cl_2/MeOH (99.5:0.5). ^{1}H NMR ($CDCl_3$): δ 7.85 (dd, 2H), 7.20 (d, 2H), 7.08 (t, 2H), 6.80 (d, 2H), 6.35 (t, 1H), 4.50 (d, 2H), 4.20 (q, 2H), 2.63 (s, 3H), 1.55 (s, 6H), 1.23 (t, 3H).

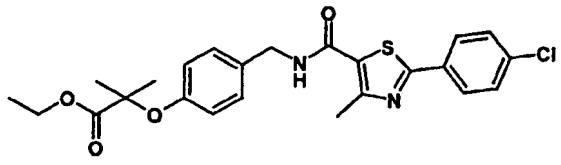


Example 31:

2-methyl-2-[4-{[(4-methyl-2-[4-fluorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **30** was reacted as described in general procedure 8 to afford the title compound as a white solid (72%).

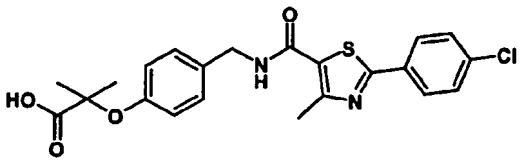
Mp 159°C; MS m/z 429 (M+1)



Example 32:

2-methyl-2-[4-{[(4-methyl-2-[4-chlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **33** and Intermediate **68** were reacted as described in general procedure 7 to afford the title compound as a clear oil (78%). Chromatographed: CH_2Cl_2, then CH_2Cl_2/MeOH (99:1). ^1H NMR ($CDCl_3$): δ 7.75 (d, 2H), 7.35 (d, 2H), 7.15 (d, 2H), 6.75 (d, 2H), 6.05 (t, 1H), 4.45 (d, 2H), 4.20 (q, 2H), 2.65 (s, 3H), 1.50 (s, 6H), 1.20 (t, 3H).

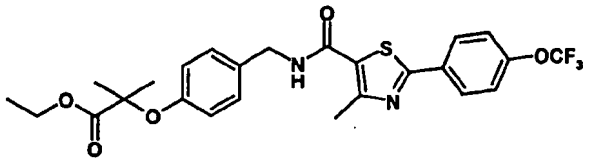


Example 33:

2-methyl-2-[4-{[(4-methyl-2-[4-chlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **32** was reacted as described in general procedure 8 to afford the title compound as a white solid (30%).

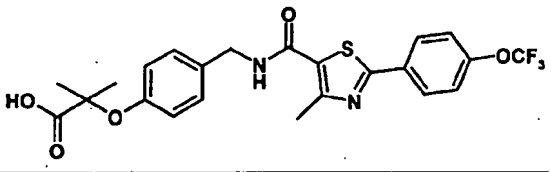
Mp 131°C



Example 34:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

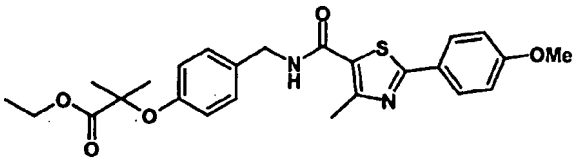
Intermediate **34** and Intermediate **68** were reacted as described in general procedure 6 to afford the title compound as a yellow oil (41%). Chromatographed: CH_2Cl_2/MeOH (99.5:0.5). ^1H NMR ($CDCl_3$): δ 7.90 (d, 2H), 7.20 (d, 2H), 7.15 (d, 2H), 6.75 (d, 2H), 6.05 (t, 1H), 4.45 (d, 2H), 4.15 (q, 2H), 2.65 (s, 3H), 1.50 (s, 6H), 1.20 (t, 3H).



Example 35:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

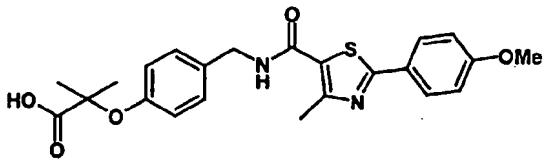
Example **34** was reacted as described in general procedure 8 to afford the title compound as a brown viscous oil (45%). ^1H NMR ($CDCl_3$): δ 7.85 (d, 2H), 7.20 (d, 2H), 7.20 (d, 2H), 6.85 (d, 2H), 6.05 (t, 1H), 4.50 (d, 2H), 2.65 (s, 3H), 1.50 (s, 6H).



Example 36:

2-methyl-2-[4-{[(4-methyl-2-[4-methoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **35** and Intermediate **68** were reacted as described in general procedure 6 to afford the title compound as a clear oil that solidified on standing (22%). Chromatographed: cyclohexane/EtOAc (1:1). ^1H NMR (DMSO-d_6): δ 8.75 (t, 1H), 7.90 (d, 2H), 7.20 (d, 2H), 7.05 (d, 2H), 6.75 (d, 2H), 4.35 (d, 2H), 4.15 (q, 2H), 3.80 (s, 3H), 2.55 (s, 3H), 1.50 (s, 6H), 1.15 (t, 3H).

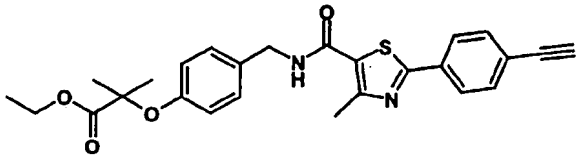


Example 37:

2-methyl-2-[4-{[(4-methyl-2-[4-methoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **36** was reacted as described in general procedure 8 to afford the title compound as a beige solid (51%).

MS m/z 441 (M+1)

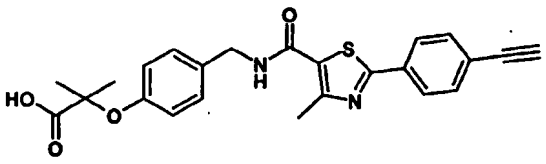


Example 38:

2-methyl-2-[4-{[(4-methyl-2-[4-acetylenylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **38** and Intermediate **68** were reacted as described in general procedure 6 to afford the title compound as a brown oil that solidified on standing (84%). Chromatographed: CH_2Cl_2/EtOAc (95:5).

MS m/z 463 (M+1)

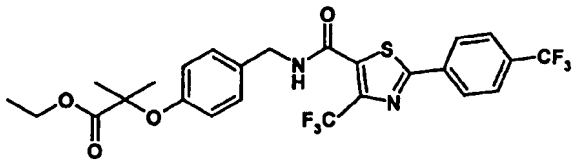


Example 39:

2-methyl-2-[4-{[(4-methyl-2-[4-acetylenylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **38** was reacted as described in general procedure 8 to afford the title compound as a pale rose solid (44%).

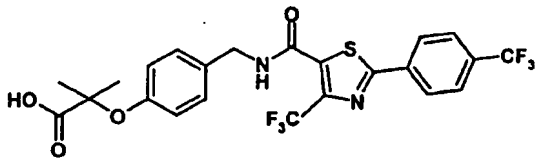
MS (AP-) m/z 433 (M-1)



Example 40:

2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

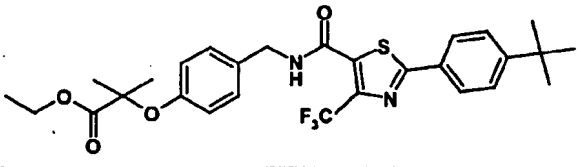
Intermediate **42** and Intermediate **68** were reacted as described in general procedure 7 to afford the title compound as a clear oil (69%). Chromatographed: CH_2Cl_2. ^1H NMR ($CDCl_3$): δ 8.00 (d, 2H), 7.65 (d, 2H), 7.15 (d, 2H), 6.75 (d, 2H), 6.35 (t, 1H), 4.50 (d, 2H), 4.15 (q, 2H), 1.50 (s, 6H), 1.20 (t, 3H).



Example 41:

2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

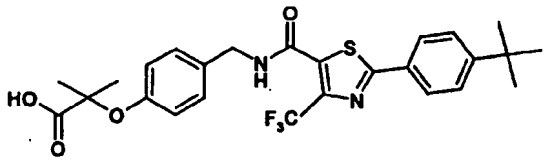
Example **40** was reacted as described in general procedure 8 to afford the title compound as a clear oil that precipitated in pentane as a white solid (19%). Chromatographed: CH_2Cl_2/MeOH (95:5), then CH_2Cl_2/MeOH/AcOH (95:5:2mL). ^1H NMR (DMSO-d_6): δ 9.55 (t, 1H), 8.25 (d, 2H), 8.00 (d, 2H), 7.25 (d, 2H), 6.85 (d, 2H), 4.45 (d, 2H), 1.55 (s, 6H).



Example 42:

2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **42** and Intermediate **68** were reacted as described in general procedure 7 to afford the title compound as a clear oil (21%). Chromatographed: CH_2Cl_2. ^1H NMR ($CDCl_3$): δ 7.85 (d, 2H), 7.45 (d, 2H), 7.25 (d, 2H), 6.85 (d, 2H), 6.40 (t, 1H), 4.60 (d, 2H), 4.25 (q, 2H), 1.60 (s, 6H), 1.35 (s, 9H), 1.25 (t, 3H).

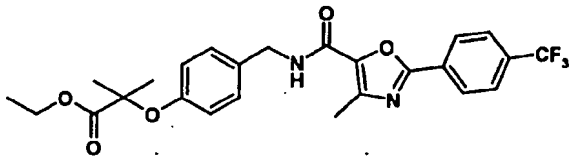


Example 43:

2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **42** was reacted as described in general procedure 8 to afford the title compound as a clear oil that precipitated in pentane as a white solid (100%).

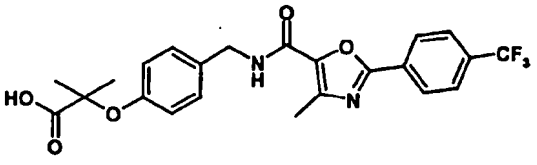
MS m/z 521 (M+1)



Example 44:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethylphenyl]-oxazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **52** and Intermediate **68** were reacted as described in general procedure 7 to afford the title compound as a clear oil (58%). Chromatographed: CH_2Cl_2/MeOH (99.5:0.5). ^1H NMR ($CDCl_3$): δ 8.05 (d, 2H), 7.65 (d, 2H), 7.25 (t, 1H), 7.15 (d, 2H), 6.75 (d, 2H), 4.50 (d, 2H), 4.15 (q, 2H), 2.70 (s, 3H), 1.50 (s, 6H), 1.20 (t, 3H).

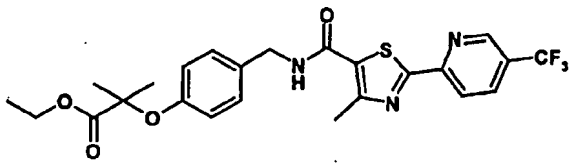


Example 45:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-oxazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **44** was reacted as described in general procedure 8 to afford the title compound as a yellow solid (98%).

MS (AP-) m/z 461 (M-1)

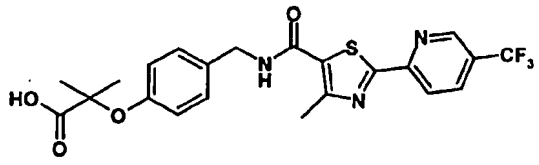


Example 46:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethyl-2-pyridyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **54** and Intermediate **68** were reacted as described in general procedure 6 to afford the title compound as a clear oil (58%). Chromatographed: CH_2Cl_2/MeOH (99.5:0.5).

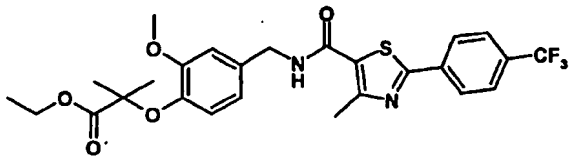
MS m/z 508 (M+1)



Example 47:

2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethyl-2-pyridyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **46** was reacted as described in general procedure 8 to afford the title compound as a white solid (11%; mixture of the free base and hydrochloride salt). ^{1}H NMR ($CDCl_3$): δ 8.75 (s, 1H), 8.20 (d, 2H), 7.95 (d, 2H), 7.15 (d, 2H), 6.85 (d, 2H), 6.20 (t, 1H), 4.45 (d, 2H), 2.65 (s, 3H), 1.50 (s, 6H).

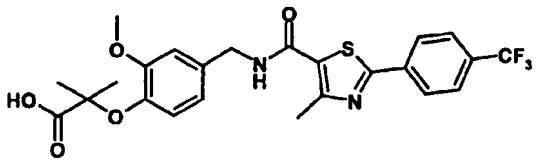


Example 48:

2-methyl-2-[2-methoxy-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **3** and Intermediate **57** were reacted as described in general procedure 6 to afford the title compound as a clear oil (37%).

MS m/z 537 (M+1)

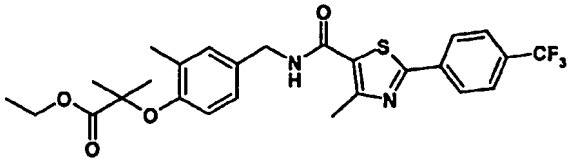


Example 49:

2-methyl-2-[2-methoxy-4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **48** was reacted as described in general procedure 8 to afford the title compound as a white solid (53%).

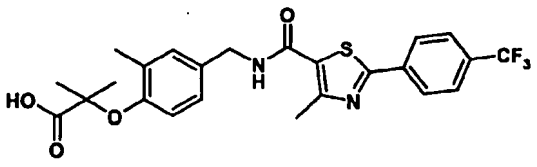
MS m/z 508



Example 50:

2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **3** and Intermediate **63** were reacted as described in general procedure 6 to afford the title compound as a white solid (33%). ^{1}H NMR ($CDCl_3$): δ 7.95 (d, 2H), 7.65 (d, 2H), 7.05 (d, 1H), 6.95 (dd, 1H), 6.55 (d, 1H), 5.95 (t, 1H), 4.45 (d, 2H), 4.15 (q, 2H), 2.65 (s, 3H), 2.15 (s, 3H), 1.50 (s, 6H), 1.15 (t, 3H).

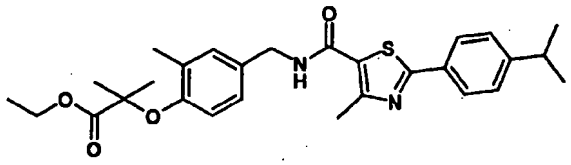


Example 51:

2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **50** was reacted as described in general procedure 8 to afford the title compound as a white solid (93%).

MS m/z 493 (M+1)

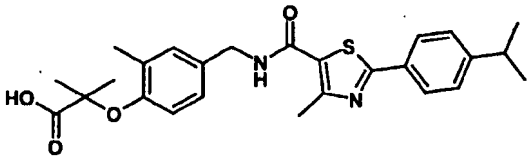


Example 52:

2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **25** and Intermediate **63** were reacted as described in general procedure 6 to afford the title compound as a white solid (51%).

Mp 129-131°C

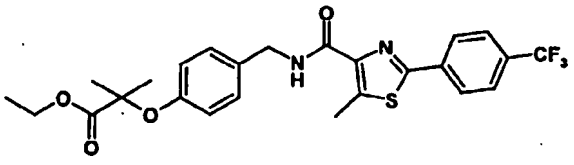


Example 53:

2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **52** was reacted as described in general procedure 8 to afford the title compound as a white solid (85%).

MS m/z 467 (M+1)

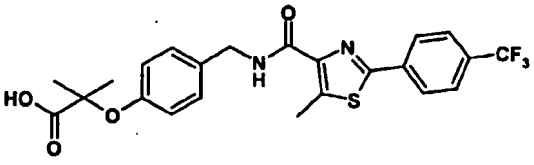


Example 54:

2-methyl-2-[4-{[(5-methyl-2-[4-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **44** and Intermediate **68** were reacted as described in general procedure 6 to afford the title compound as a white solid (85%).

MS m/z 507 (M+1)

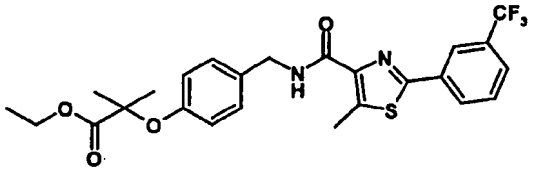


Example 55:

2-methyl-2-[4-{[(5-methyl-2-[4-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **54** was reacted as described in general procedure 8 to afford the title compound as a white solid (39%).

MS m/z 479 (M+1)

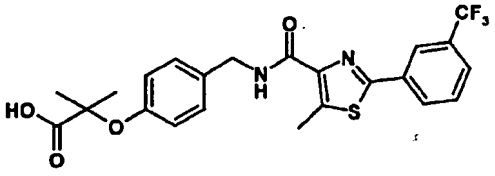


Example 56:

2-methyl-2-[4-{[(5-methyl-2-[3-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

Intermediate **25** and Intermediate **63** were reacted as described in general procedure 6 to afford the title compound as a pale yellow oil (43%).

MS m/z 507 (M+1)



Example 57:

2-methyl-2-[4-{[(5-methyl-2-[3-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid

Example **56** was reacted as described in general procedure 8 to afford the title compound as a white solid (74%).

MS m/z 479 (M+1)

The following Intermediates and ligands were prepared for the binding and transfection assays described below.

(i) 2-(4-(2-(2,3-ditritio-1-heptyl-3-(2,4-difluorophenyl)ureido)ethyl)phenoxy)-2-methylbutanoic acid

This compound was used as a control radioligand for hPPARα in the binding assay described below. It is also described in WO00/08002, the synthesis is reproduced below;

Intermediate A: 2-(4-(2-(Phenylmethyloxycarbonylamino)ethyl) phenoxy)-2-methylbutanoic acid

A solution of 4-(2-(phenylmethyloxycarbonylamino)ethyl)phenol (5.74 g; 21.16 mmole) in 2-butanone (17 mL) and chloroform (6 g) was added dropwise to a mixture of sodium hydroxide (9.0 g; 225 mmole) and 2-butanone (67 mL) whilst keeping the reaction temperature below 30°C. The mixture was allowed to stir at 30°C for 4h. Ether (100 mL) was added and the resultant solid was collected by filtration and washed with ether (100 mL). The solid was dissolved in water (70 mL) and any residual ether removed by evaporation. 1N Hydrochloric acid was added to adjust the pH to 1, and the resulting oil was extracted with dichloromethane (3 x 50 mL). The combined extracts were dried (Na_2SO_4) and evporated to afford a yellow oil (3.82 g; 49%). ^{1}H-NMR ($CDCl_3$) δ 7.26 (s, 5H), 7.09 (d, 2H, J=7.9 Hz), 6.88 (d, 2H, J=8.4 Hz), 5.09 (s, 2H), 4.75 (br s, 1H), 3.42-3.44 (m, 2H), 2.75 (t, 2H, J=6.7 Hz), 1.92-2.00 (m, 2H), 1.47 (s, 3H), 1.04 (t, 3H, J=2.6 Hz). Mass spectrometry ES$^-$, m/e $(M+H)^+$=372.

Intermediate B: Methyl 2-(4-(2-(phenylmethyloxycarbonylamino) ethyl)phenoxy)-2-methyl butyrate

A solution of Intermediate A (2.0 g; 5.38 mmole) in dimethylformamide (12 mL) was treated with potassium carbonate (2.23 g; 16.14 mmole) and methyl iodide (1.54 g; 10.76 mmole) and the resulting mixture stirred at 23°C for 2h. The mixture was filtered and the solid collected was washed with ethyl acetate (70 mL). The filtrate was washed with brine (4 x 50 mL), dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel using hexane then 33% ethyl acetate-hexane as eluent to afford a colorless oil (1.27 g; 61%).

^{1}H-NMR (DMSO-d_6) δ 7.31 (m, 5H), 7.06 (d, 2H, J=8.4 Hz), 6.68 (d, 2H, J=8.4 Hz), 4.98 (s, 2H), 3.67 (s, 3H), 3.15 (m, 2H), 2.62 (t, 2H, J=7.1 Hz), 1.86 (m, 2H), 1.38 (s, 3H), 0.86 (t, 3H, J=7.3 Hz). Mass spectrometry ES$^+$, m/e $(M+Na)^+$ = 408.

Intermediate C: Methyl 2-(4-(2-aminoethyl)phenoxy)-2-methyl butyrate acetate salt

A solution of Intermediate B (1.27 g; 3.29 mmole) in methanol (50 mL) and acetic acid (0.4 g) was treated with 10% palladium on carbon and shaken in a hydrogen atmosphere (50 psi) for 2h. The catalyst was filtered through celite and the solvent was evaporated to afford a yellow oil in quantitative yield (1.04 g).

^{1}H-NMR ($CDCl_3$): δ 7.06 (d, 2H, J=8.4 Hz), 6.77 (d, 2H, J=8.4 Hz), 6.70 (br s, 2H), 3.76 (s, 3H), 3.02 (br s, 2H), 2.82 (m, 2H), 1.99 (s, 3H), 1.92 (m, 2H), 1.48 (s, 3H), 0.96 (t, 3H, J=7.4 Hz). Mass spectrometry ES^+, m/e $(M+H)^+$=252.

Intermediate D: Methyl 2-(4-(2-(2,4-dinitrophenylsulfonylamino)ethyl)phenoxy)-2-methyl butyrate

A solution of Intermediate C (2 g; 6.42 mmole) in CH_2Cl_2 (40 mL) was treated with saturated sodium bicarbonate solution and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (5 x 50 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated to afford the free base as a yellow oil (1.61 g; 100%). This was dissolved in CH_2Cl_2 (40 mL) and treated with pyridine (0.45 g; 5.61 mmole) and 2,4-dinitrophenylsulfonyl chloride (1.5 g; 5.61 mmole), and the mixture was allowed to stir at 23°C for 3h. Water (60 mL) was added and the organic layer separated, washed with water (3 X 40 mL) and saturated sodium bicarbonate (40 mL). The organic layer was dried (Na_2SO_4) and evaporated and the residue purified by chromatography using 15-20% EtOAc-Hexane as eluent to afford a light yellow solid (1.38 g; 51%). ^{1}H-NMR ($CDCl_3$): δ 8.63 (d, 1H, J=2.3 Hz), 8.49 (dd, 1H, J=8.4 Hz, J'=2.3 Hz), 8.07 (d, 1H, J=8.4 Hz), 6.89 (d, 2H, J=8.4 Hz), 6.54 (d, 2H, J=8.4 Hz), 5.34 (t, 1H, J=5.3 Hz), 3.78 (s, 3H), 3.48 (q, 2H, J=8.3 Hz), 2.75 (t, 2H, J=6.6 Hz), 1.92 (m, 2H), 1.42 (s, 3H), 0.93 (t, 3H, J=7.5 Hz).

Intermediate E: Methyl 2-(4-(2-((2,4-dinitrophenylsulfonyl)(hept-2-en-1-yl))amino)ethyl)phenoxy)-2-methyl butyrate

A solution of Intermediate D (315 mg; 0.654 mmole) in THF (15 mL) was treated with triphenylphosphine (343 mg; 1.308 mmole), hept-2-en-1-ol (150 mg; 1.308 mmole) and diethylazodicarboxylate (228 mg; 1.308 mmole) and the mixture allowed to stir at 23°C for 1h. The solvent was evaporated and the residue purified by chromatography using 10-15% EtOAc-Hexane as eluent to

afford a semi-solid (400 mg; >100%). TLC and NMR shows that the desired compound is present along with 1,2-(diethoxycarbonyl)hydrazine.

Intermediate F: Methyl 2-(4-(2-(hept-2-en-1-ylamino)ethyl)phenoxy)-2-methyl butanoate

A solution of Intermediate E (400 mg; 0.654 mmole) in CH_2Cl_2 (5 mL) was treated with triethylamine (132 mg; 1.308 mmole) and mercaptoacetic acid (78 mg; 0.85 mmole) and the mixture was allowed to stir at 23°C for 1h. The mixture was diluted with EtOAc (30 mL) and washed with water (3 X 20 mL) and aqueous sodium bicarbonate (30 mL). The organic layer was dried (Na_2SO_4), evaporated and the residue purified by chromatography using 10% EtOAc-Hexane then 50% EtOAc-Hexane then MeOH as eluent to afford an oil (177 mg; 78% from intermediate 24).

^{1}H-NMR ($CDCl_3$): δ 7.06 (d, 2H, J=7.5 Hz), 6.75 (d, 2H, J=7.5 Hz), 5.59 (m, 2H), 3.76 (s, 3H), 3.30 (d, 2H, J=6.3 Hz), 2.87 (m, 4H), 1.96 (m, 4H), 1.47 (s, 3H), 1.28 (m, 5H), 0.96 (t, 3H, J=7.6 Hz), 0.86 (t, 3H, J=6.9 Hz).

Intermediate G: Methyl 2-(4-(2-(1-hept-2-enyl-3-(2,4-difluorophenyl)ureido)ethyl)phenoxy)-2-methylbutyrate

A solution of Intermediate F (157 mg; 0.452 mmole) in methylene chloride (5 mL) was treated with 2,4-difluorophenylisocyanate (140 mg; 0.904 mmole) and the mixture allowed to stand at 23°C for 18h. The solvent was evaporated and the residue purified by chromatography on silica gel using 10% then 15% ethyl acetate-hexane as eluent to afford a yellow semi-solid (212 mg; 93%). Contaminated with bis-(2,4-difluorophenyl)urea which co-elutes on column.

^{1}H-NMR ($CDCl_3$): δ 8.85 (br s, 1H), 8.02 (m, 1H), 7.09 (d, 2H, J=8.4 Hz), 6.77-6.90 (m, 4H), 5.70 (m, 1H), 5.36 (m, 1H), 3.76 (s, 3H), 3.54 (t, 2H, J=7.3 Hz), 2.84 (t, 2H, J=7.1 Hz), 1.55 (br s, 1H), 1.46 (s, 3H), 1.25-1.35 (m, 5H), 0.96 (t, 3H, J=7.3 Hz), 0.88 (t, 3H, J=7.4 Hz). Mass spectrometry CI/AP$^+$, m/e $(M+H)^+$=503.

2-(4-(2-(1-Hept-2-enyl-3-(2,4-difluorophenyl)ureido)ethyl) phenoxy)-2-methylbutanoic acid (Radioligand Precursor)

A solution of Intermediate G (370 mg; 0.736 mmole) in methanol (15 mL) was treated with 1N NaOH (7.5 mL) and the mixture heated under reflux for

2h. The mixture was acidified with 1N HCl and extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. The residue was purified by chromatography on silica gel using 20% ethyl acetate-hexane then ethyl acetate as eluent to afford a tan oil (280 mg; 78%).

^{1}H-NMR ($CDCl_3$) δ 7.95-8.09 (m,1H), 7.14 (d, 2H, J=7.1 Hz), 6.90 (d, 2H, J=7.4 Hz), 6.81 (d, 2H, J=5.2 Hz), 5.66 (m, 1H), 5.37 (m,1H), 3.56 (t, 2H, J=7.4 Hz), 2.87 (t, 2H, J=7.4 Hz), 2.00 (m, 4H), 1.44 (s, 3H), 1.27 (m, 6H), 1.03 (t, 3H, J=7.3 Hz), 0.88 (t, 3H, J=7.3 Hz). Mass spectrometry ES$^-$, m/e $(M+H)^+$ = 489.

Radioligand: 2-(4-(2-(2,3-Ditritio-1-heptyl-3-(2,4-difluorophenyl)ureido)ethyl) phenoxy)-2-methylbutanoic acid

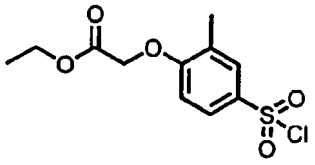
A solution of radioligand precursor prepared above (10 mg) in anhydrous DMF (3.5 mL) was transferred to a reaction vessel containing 10 % Pd/C (9.8 mg). The reaction vessel was evacuated and degassed via one freeze-thaw-evacuation cycle and then exposed to tritium gas (10.1 Ci). After 4h, the mixture was filtered through celite, evaporated and the residue dissolved in acetonitrile. A portion of this solution (0.8 mL, 26.6 mCi) was purified by HPLC (Dynamax C8, 25 min gradient from 4:1 acetonitrile:0.1%TFA to 9:1 acetonitrile: 0.1% TFA, 235 nm). Fractions containg pure material were combined and evaporated under nitrogen. The residue was redissolved in acetonitrile to provide a solution of the title compound (82.0 Ci/mmol, radiochemical purity, 99%).

2-(4-(2-(1-Heptyl-3-(2,4-difluorophenyl)ureido)ethyl) phenoxy)-2-methylbutanoic acid

The unlabelled ("cold") version of the above radioligand was prepared as a control. A solution of Intermediate G (10 mg) in anhydrous DMF (3.5 mL) was transferred to a reaction vessel containing 10 % Pd/C (9.8 mg). The reaction vessel was evacuated and degassed via one freeze-thaw-evacuation cycle and then exposed to hydrogen gas. After 4h, the mixture was filtered through celite and evaporated. The residue was purified by chromatography using 2% $MeOH/CH_2Cl_2$ as eluent to afford a gum (7mg).

(ii) 2-{2-methyl-4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid

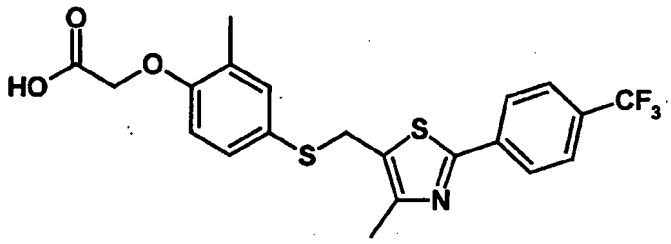
This compound was used as a positive control for PPAR delta in the transfaction assay and may be prepared as demonstrated below:



Intermediate H

Chlorosulfonic acid (15mL) was cooled to 0°C. then 10.0 g (0.05M) of ethyl (2-methylphenoxyacetate was added over 10 m. The reaction mixture was stirred at 0-5°C for 30m, the bath was removed and stirring continued for 2 h. The reaction mixture was poured into ice, forming a white solid which was washed with ice water and dried under high vacuum affording the title compound (12.846 g ,86%).

2-{2-methyl-4-[({4-methyl-2-[4-(trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid

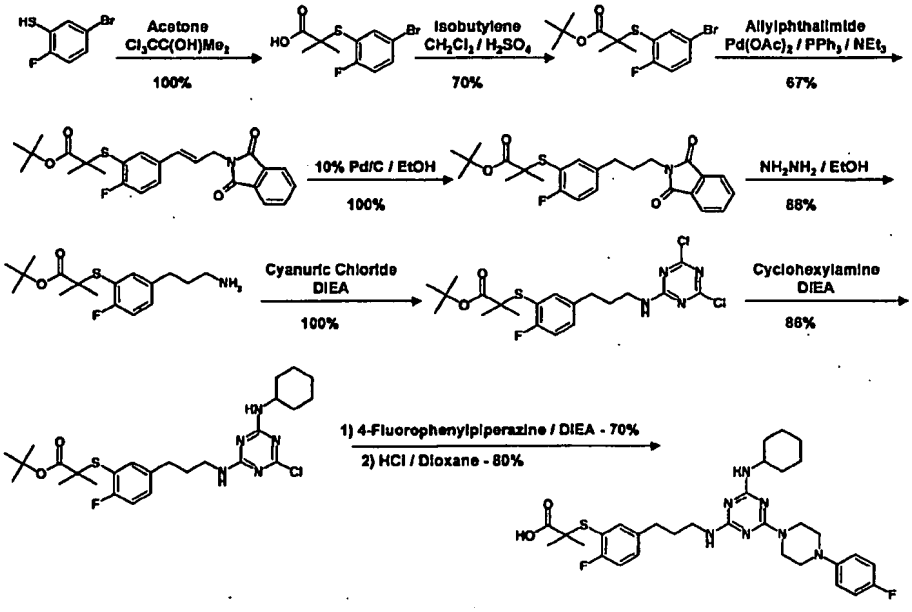


Intermediate H (4.68g, 16mM) was refluxed with 9.6 g of tin powder in ethanol (20mL) and dioxane/HCl (20 mL). After 3 h the reaction mixture was poured into ice and CH_2Cl_2 (200mL) and filtered. The phases were separated and the aqueous layer was extracted 2X 50 mL CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered and evaporated to yield 3.5g (97%). This material readily forms disulfides and therefore was used immediately. It was dissolved in acetonitrile (50mL) with intermediate 2 (4.0 g, 14.0mM) and Cs_2CO_3 (10.1 g, 31.0 mM) and stirred for 1 h then diluted with ether (200mL) and water (200mL). The phases were separated and the organic phase was washed 2X NaOH 0.1N (50mL), dried ($MgSO_4$), filtered and evaporated to afford crude

product (6.57 g,) which was slurried in hexane:ether (1:1) and filtered to yield pure intermediate 59 (5.0g, 74%). This material is then be hydrolyzed as described below to prepare the title compound. A solution of the corresponding ester (1 mmol) in THF (10 mL) (in some cases few drops of MeOH were added to help solubility), was treated with 1N LiOH in water (2 mL, 2 mmol), and stirred 16 h at room temperature (when reactions were slow, the temperature was elevated to 50°C). The solution was neutralized with 1N HCl (2 mL, 2 mmol) and the organic solvent evaporated to afford an aqueous solution with an insoluble product. If the insoluble was a solid, it was filtered and dried to afford the final product. If the insoluble was an oil, it was extracted with EtOAc (30 mL). The organic solution was separated, washed with water (2 x 30 mL), dried, filtered, and evaporated to afford the final product.

(iii) 2-(2-methyl-3-[3-{3-(4-cyclohexylamino)-[6-(4-fluorophenylpiperazin-1-yl)][1,3,5]triazin-2-ylamino}propyl]phenylthio)-2-methylpropionic acid

This compound was used as a PPARalpha reference in the transfection assays described below and as prepared according to the following method:



Binding Assay:

Compounds were tested for their ability to bind to hPPAR gamma hPPAR alpha, or PPAR delta using a Scintillation Proximity Assay (SPA). The PPAR ligand binding domain (LBD) was expressed in *E. coli* as polyHis tagged fusion proteins and purified. The LBD was then labeled with biotin and immobilized on streptavidin-modified scintillation proximity beads. The beads were then incubated with a constant amount of the appropriate radioligand (^{3}H-BRL 49653 for PPAR gamma, radiolabelled 2-(4-(2-(2,3-Ditritio-1-heptyl-3-(2,4-difluorophenyl)ureido)ethyl)phenoxy)-2-methylbutanoic acid for hPPAR alpha and labelled GW 2433 for PPAR delta (see Brown, P. J et al . *Chem. Biol.* **1997**, *4*, 909-918. For the structure and synthesis of this ligand)) and variable concentrations of test compound, and after equilibration the radioactivity bound to the beads was measured by a scintillation counter. The amount of nonspecific binding, as assessed by control wells containing 50 μM of the corresponding unlabeled ligand, was subtracted from each data point. For each compound tested, plots of ligand concentration vs. CPM of radioligand bound were constructed and apparent K_i values were estimated from nonlinear least squares fit of the data assuming simple competitive binding. The details of this assay have been reported elsewhere (see, Blanchard, S. G. et. al. Development of a Scintillation Proximity Assay for Peroxisome Proliferator-Activated Receptor gamma Ligand Binding Domain. *Anal. Biochem.* **1998**, *257*, 112-119).

Transfection assay:

Compounds were screened for functional potency in transient transfection assays in CV-1 cells for their ability to activate the PPAR subtypes (transactivation assay). A previously established chimeric receptor system was utilized to allow comparison of the relative transcriptional activity of the receptor subtypes on the same target gene and to prevent endogenous receptor activation from complicating the interpretation of results. See, for example, Lehmann, J. M.; Moore, L. B.; Smith-Oliver, T. A.; Wilkison, W. O.; Willson, T. M.; Kliewer, S. A., An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ), *J. Biol. Chem.*, **1995**, *270*, 12953-6. The ligand binding domains for murine and human PPAR alpha, PPAR gamma, and PPAR delta were each fused to the yeast transcription factor GAL4 DNA binding domain. CV-1 cells were transiently transfected with expression vectors for the respective PPAR chimera along with a reporter construct

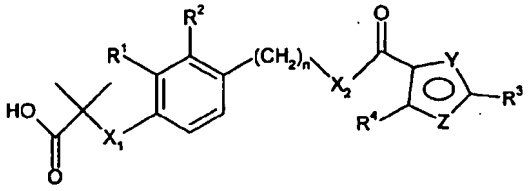
containing five copies of the GAL4 DNA binding site driving expression of secreted placental alkaline phosphatase (SPAP) and β-galactosidase. After 16 h, the medium was exchanged to DME medium supplemented with 10% delipidated fetal calf serum and the test compound at the appropriate concentration. After an additional 24 h, cell extracts were prepared and assayed for alkaline phosphatase and β-galactosidase activity. Alkaline phosphatase activity was corrected for transfection efficiency using the β-galactosidase activity as an internal standard (see, for example, Kliewer, S. A., et. al. *Cell 83*, 813-819 (1995)). Rosiglitazone (BRL 49653) was used as a positive control in the hPPAR gamma assay. The positive control in the hPPAR alpha assays was 2-(2-methyl-3-[3-{3-(4-cyclohexylamino)-[6-(4-fluorophenylpiperazin-1-yl)][1,3,5]triazin-2-ylamino}propyl]phenylthio)-2-methylpropionic acid. The positive control for PPAR delta assays was 2-{2-methyl-4-[({4-methyl-2-{trifluoromethyl)phenyl]-1,3-thiazol-5-yl}methyl)sulfanyl]phenoxy}acetic acid.

Table 2. PPAR Transactivation activity for selected compounds.

Example no.	human αEC_{50} μM	human δEC_{50} μM	human γEC_{50} μM
Example 1	0.017	10.000	10.000
Example 2	0.005	2.950	10.000
Example 6	0.230	10.000	10.000
Example 10	0.108	10.000	10.000
Example 13	0.005	10.000	0.850
Example 16	0.001	4.370	2.640
Example 17	0.027	10.000	10.000
Example 21	0.028	10.000	10.000
Example 23	0.007	9.190	10.000
Example 26	0.010	2.700	10.000
Example 27	0.002	4.080	8.820
Example 29	0.122	10.000	10.000
Example 31	0.044	10.000	10.000
Example 33	0.014	6.350	10.000
Example 35	0.004	4.590	10.000
Example 37	0.020	10.000	10.000
Example 39	0.036	2.480	10.000
Example 41	0.005	10.000	0.832
Example 45	0.400	1.640	10.000
Example 47	0.020	7.300	10.000
Example 49	0.010	1.000	10.000

What is claimed is:

1. A compound of formula (I) and pharmaceutically acceptable salts, solvates and hydrolysable esters thereof



(I)

wherein;

X_1 represents O or S;
R^1 and R^2 independently represent H, halogen, $-CH_3$ and $-OCH_3$;
n represents 1 or 2;
X_2 represents NH, NCH_3 or O;
One of Y and Z is N, and the other is O or S;
R^3 represents phenyl or pyridyl (wherein the N is in position 2 or 3) and is optionally substituted by one or more halogen, NO_2, NH_2, CF_3, OCF_3, OC_{1-6}straight or branched alkyl, C_{1-6} straight or branched alkyl, alkenyl or alkynyl with the provision that when R^3 is pyridyl, the N is unsubstituted;
R^4 represents CF_3 or CH_3

2. A compound of formula (I) which is a hPPAR alpha agonist.

3. A compound according to claim 2 which is a selective hPPAR alpha agonist.

4. A compound according to claims 1-3 wherein X_1 represents O.

5. A compound according to claims 1-4 wherein one of R^1 and R^2 is H.

6. A compound according to claim 5 wherein R^1 and R^2 both represent H.

7. A compound according to any of claims 1-6 wherein n represents 1.

8. A compound according to any of claims 1-7 wherein X_2 represents NH.

9. A compound according to claims 1-8 wherein Z represents N.

10. A compound according to claims 1-9 wherein Y represents S.

11. A compound according to any of claims 1-10 wherein R^3 is monosubstituted.

12. A compound according to claim 11 where R^3 is monosubstituted with CF_3.

13. A compound according to claim 11 or 12 wherein R^3 is monosubstituted in the para position.

14. A compound according to any previous claim wherein R^3 is phenyl.

15 A compound according to any preceding claim wherein R^4 is CH_3.

16. A compound selected from:
2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid ethyl ester
N-methyl-2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid ethyl ester
4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-carboxylic acid 4-(1-tertbutyloxycarbonyl-1-methylethoxy) benzyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-nitrophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-aminophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[4-{[(4-methyl-2-[4-aminophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[3,4-dichlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[3-fluoro-4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-bromophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-ethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-phenylthiazol-5-ylcarbonyl)amino]-methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-fluorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-chlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-methoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-acetylenylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethylphenyl]-oxazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethyl-2-pyridyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[2-methoxy-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester

2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[2-methyl-4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(5-methyl-2-[4-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(5-methyl-2-[4-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(5-methyl-2-[3-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(5-methyl-2-[3-trifluoromethylphenyl]-thiazol-4-ylcarbonyl)amino]methyl}phenoxy]propionic acid

17. A compound selected from:
2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid ethyl ester
2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid
N-methyl-2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]ethyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-tertbutylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-isopropylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-nitrophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[3,4-dichlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[3-fluoro-4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

2-methyl-2-[4-{[(4-methyl-2-[4-bromophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-ethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-phenylthiazol-5-ylcarbonyl)amino]-methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-fluorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-chlorophenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-methoxyphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-acetylenylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-trifluoromethyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethylphenyl]-oxazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[4-{[(4-methyl-2-[4-trifluromethyl-2-pyridyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid
2-methyl-2-[2-methoxy-4-{[(4-methyl-2-[4-trifluromethylphenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid

18. 2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]thiazol-5-ylcarbonyl)-amino]methyl}phenoxy]propionic acid.

19. A compound according to any of claims 1-17 for use in therapy.

20. A pharmaceutical composition comprising a compound according to any of claims 1-17.

21. A pharmaceutical composition according to claim 20 further comprising a pharmaceutically acceptable diluent or carrier.

22. Use of a compound according to any of claims 1-17 for the manufacture of a medicament for the treatment of a hPPAR alpha disease or condition.

23. Use according to claim 22 wherein the hPPAR alpha mediated disease or condition is dyslipidemia, syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, inflammation, anorexia bulimia and anorexia nervosa

24. A method of treating a hPPAR alpha mediated disease or condition in a patient comprising the administration of a therapeutically effective amount of a compound according to any of claims 1-17.

25. A method according to claim 24 wherein the hPPAR alpha mediated disease or condition is dyslipidemia, syndrome X, heart failure, hypercholesteremia, cardiovascular disease, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidemia, obesity, inflammation, anorexia bulimia and anorexia nervosa.

INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 00/11995

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D277/56 C07D263/34 C07D401/04 A61K31/426 A61K31/421
A61P3/06 A61P9/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 18066 A (SANKYO CO) 15 April 1999 (1999-04-15) the whole document	1-25
P,A	& EP 1 026 149 A 9 August 2000 (2000-08-09)	1-25
A	WO 99 46232 A (ONO PHARMACEUTICAL CO) 16 September 1999 (1999-09-16) the whole document	1-25
E	& EP 1 067 109 A 10 January 2001 (2001-01-10)	1-25
A	WO 97 36579 A (GLAXO GROUP LTD ;WILLSON TIMOTHY MARK (US)) 9 October 1997 (1997-10-09) the whole document	1-25

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2001	27.03.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, J-C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ırnational application No.
PCT/EP 00/11995

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 24,25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/EP 00/11995

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9918066 A	15-04-1999	AU 9279898 A	27-04-1999
		BR 9813019 A	05-09-2000
		CN 1280561 T	17-01-2001
		EP 1026149 A	09-08-2000
		NO 20001689 A	31-05-2000
		PL 339660 A	02-01-2001
WO 9946232 A	16-09-1999	AU 3275999 A	27-09-1999
		EP 1067109 A	10-01-2001
WO 9736579 A	09-10-1997	AU 2506197 A	22-10-1997
		US 6028109 A	22-02-2000